Review Article

Scientific Aspects of the Therapeutic Use of *Andrographis paniculata* (kalmegh): A Review

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ABSTRACT

Andrographis paniculata has been used for centuries as a medicinal herb for the treatment of upper gastrointestinal tract and upper respiratory infections, fever, herpes and other chronic diseases. It is widely used in Ayurveda as a popular remedy for the treatment of various liver disorders. Phytochemical investigation of this well studied herb showed that it is a rich source of bioactive flavonoids and diterpenoids. The structures of these compounds have been established on the basis of various spectral studies. Detailed research regarding the phytochemical and pharmacological aspects of the *A. paniculata* leads to the fact that it is a valuable source of unique natural products for various medicinal applications. The main objective of this article is to review the literature of *A. paniculata* specifically articles pertaining to therapeutic benefits, chemical properties, pharmacological evaluation and toxicity.

Keywords: *Andrographis paniculata*, flavonoids, diterpenoids, natural products.

INTRODUCTION

Medicinal plants are the major sources for the therapeutic remedies of various ailments. Their active phytocostituents are mainly responsible for these potential medicinal effects. The genus *Andrographis* (family Acanthaceae) includes 28 species of small shrubs occurring in tropical Asian countries. Of theses *Andrographis paniculata* NEES is the most important medicinal plant and having been widely used in Chinese traditional medicines[1]. It is an annual and branched plant with lanceolate green leaves and attains heights of 60-70 cm[2]. It grows abundantly in Asian countries like India, Sri Lanka, Pakistan, Java, Malaysia and Indonesia. In India it is commonly known as Kalmegh mainly found in the plains of the country and is one of the commonly used medicinal plants in Ayurvedic and Unani systems of medicines. The plant is also known as the 'king of bitters'[3,4] because it is extremely bitter in taste in every part of plant body. On the basis of literature survey it has been observed that the aerial parts (leaves and stems) of the plants are most commonly used to extract the active phytochemicals, however the whole plant or roots are mentioned to a limited extend[4]. Diterpenoids and flavonoids are the major class of secondary metabolites isolated from this plant. Therefore theses active constituents are believed to be responsible for the pharmacological properties of *A.* paniculata[5,6]. This review is aimed to summarize the knowledge concerning the phyto-pharmacological properties up to date from the plant *A. paniculata*.

Traditional uses

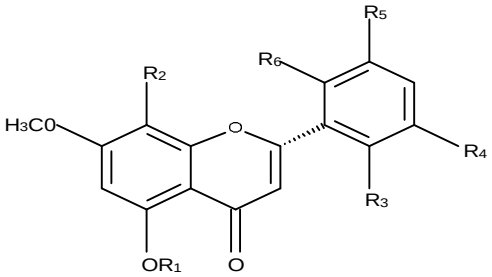
A. paniculata is one of the herbs mentioned in all ancient scriptures of Ayurveda. Extensive research has revealed that *A. paniculata* has a broad spectrum of pharmacological effects and some of them are extremely beneficial such as antimicrobial, antifungal, antioxidant, antiinflammatory, antihelmintic, antipyretic, anticancer and antidiarrhoeal effects[6]. According to Unani system of medicine it is useful in the treatment of chronic hepatitis. It is one of the most studied herbs due to its unique ability to treat various ailments like hypoglycemia, leprosy, gonorrhea, scabies, skin eruptions, hypertension, neoplasia, diuresis, dyspepsia, influenza etc. Leaves and roots are the mostly used plant parts traditionally and has been used in many European countries as a herbal supplement for health promotion. The plant has been widely used in many other Asian countries like China, Malaysia, Indonesia and Thailand for the treatment of gastric disorders, infectious diseases, common colds for many years[7].

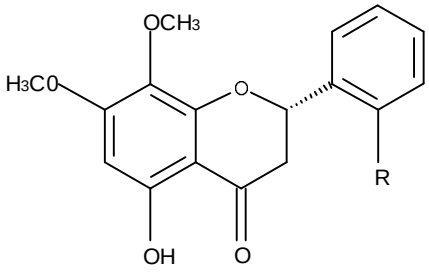
The herb *A. paniculata* which has been used in Indian medicinal practice mainly for the treatment of diabetes, dysentery, herpes, enteritis, peptic ulcer, skin infections, snake bites etc. The plant is official in Indian Pharmacopoeia as a prominent constituent of atleast 26 Ayurvedic formulations used to treat liver disorders and can be widely used to treat neoplasm as mentioned in ancient Ayurvedic literature[8,9]. Decoction of fresh leaves of the plant is given to infants to relieve griping and loss of appetite. Due to its blood purifying activity it is believed to be a good remedy for the treatment of leprosy, gonorrhea, scabies, boils, skin eruptions and chronic and seasonal fevers[10]. In addition to that pharmacological and clinical studies have demonstrated that *A. paniculata* possesses cardiovascular, immunostimulatory, adaptogenic, astringent, carminative and cytotoxic activities[11]. The traditional uses and pharmacological aspects of the plant have been well documented in an extensive review recently.

Phytochemical properties

The active phytoconstituents predominantly reported from the plant include diterpene lactones, flavonoids and

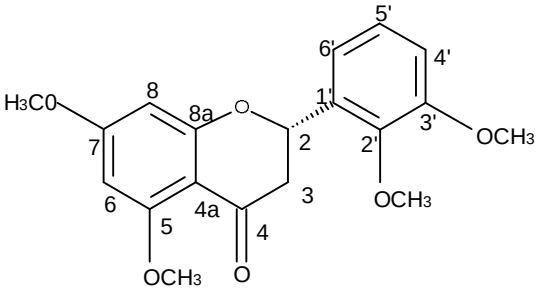
polyphenols[12]. Li et al in 2007 suggested that more than 20 diterpenoids and about 10 flavonoids have been reported from this species over the past three dacades[13,1]. The areal parts of the plant are mainly used to extract the active phytochemicals. Detailed phytochemical investigations on the chemical composition of *A. paniculata* showed that it is a rich source of 2´-oxygenated flavonoids[13-18], labdane diterpenoids [19-26], polyphenols and steroids (Fig. 1)[27,28].

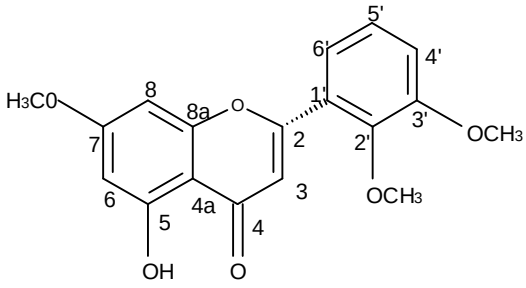


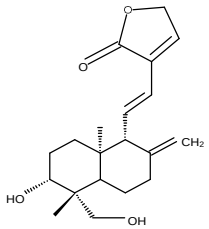


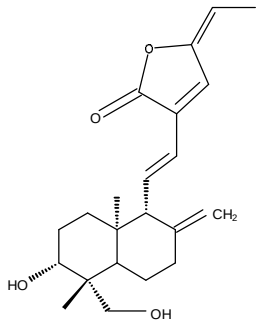
	R_1	R_2	R_3	R_4	R_5	R_6
1	H	OCH_3	H	H	H	H
2	H	OCH_3	OCH_3	H	OCH_3	H
3	H	OCH_3	OCH_3	OCH_3	H	H
4	H	H	OCH_3	H	H	OCH_3
5	H	OCH_3	OCH_3	H	H	H
6	glc	OCH_3	H	H	H	H
7	H	OCH_3	Oglc	H	H	H

	R
8	H
9	OH









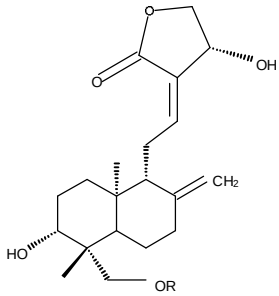


Figure 1: Structures of compounds isolated from *A. Paniculata*.

Recently several studies have been conducted to investigate the pharmacological activities of *A. paniculata* and its chemical constituents revealed andrographolide which is the prime constituent has been mainly attributed for its therapeutic potentials[29,30]. Bicyclic diterpenoid lactone andrographolide [$C_{20}H_{30}O_5$; (3-[2-{decahydro-6-hydroxy-5-(hydroxymethyl)-5,8α-dimethyl-2-methylene-1-naphthalenyl}ethylidene]dihydro-4-hydroxy-2(3H)-furanone) is mainly concentrated in leaves and can be easily isolated from the crude plant extracts as crystalline solids. It has a very bitter in taste. It is first reported from the plant in 1950's and has been reported to possess significant antitumor activity[31-33,27]. It is also exhibited anti HIV[34], cardioprotective[35], hepatoprotective[36,37,38] properties among others. GC-MS analysis of ethanolic leaf extract of *A. paniculata* observed the presence of fatty acids, fatty acid esters, di-triterpenes, steroids etc[39].

Other major compounds reported from the plant include andrographolide derivatives such as 14-deoxyandro grapholide, 14-deoxy-11-oxo-andrographolide, 14-deoxy11,12-didehydroandrographolide, andrographo sterol, neoandrographolide, homoandro grapholide,

andrographone, andrographane, andrographin, andrographosterin, andrograpanin, angrographoside, isoandrographolide and bisandrographolide flavonoids: 5-hydroxy-7,8,2',3'-tetramethoxy flavone, 5,5'-dihydroxy-7,8,2'-trimetroxyflavone, 5-hydroxy-7,8,2',6'-tetra methoxy flavone, 5,3'-dihydroxy-7, 8,4'-trimethoxy flavone, 2'-hydroxy-5,7,8-trimethoxyflavone, 5-hydroxy-7,8,2',3',4'-pentamethoxyflavone, 5,2',6'-trihydroxy-7-methoxy flavone 2'-O-beta-D-glucopyranoside, 5,7,8,2'-tetramethoxyflavone, 5-hydroxy-7,8-dimethoxyflavanone, 5-hydroxy-7,8-dimethoxyflavone, 5,2'-dihydroxy-7,8-dimethoxyflavone, 5-hydroxy-7,8,2',5'-tetramethoxy flavone, 5-hydroxy-7,8,2'-trimethoxyflavone, 5,4'-dihydroxy-7,8,2',3'-tetramethoxyflavone, 5,2'-dihydroxy-7,8-dimethoxyflavone-2'-O-beta-D-glucopyranoside and wightin, two phenylpropanoids: trans-cinnamic acid and 4-hydroxy-2-methoxycinnamaldehyde, oleanolic acid, β-sitosterol, stigmasterol, apigenin-7,4'-di-O-methyl ether etc[40,41,42].

Ent-labdane type diterpenoids were also reported from the aerial parts of the plant *A. paniculata* viz. 3-O-β-D-glucopyranosyl-14, 3-O-β-D- glucopyranosyl-andrographolide, 19-O-[β-D-apiofuranosyl (1-2)-β-D-glucopyranoyl] 3,14-dideoxy-andrographolide, 19-dideoxyandrographolide, 12S-hydroxyangrographolide, 7R-hydroxy-14-deoxy-andrographolide, 7S-hydroxy-14-deoxy-andrographolide, 12S,13S-hydroxy-andro grapholide, 12R, 13R-hydroxy -andrographolide, andrographatoside. These compounds showed significant antimicrobial activity against various bacterial and fungal strains[43,44,46]. Dua et al reported some xanthone type compounds from the roots of *A. paniculata* i.e 1,8-dihydroxy-3,7-dimethoxy xanthone, 4,8-dihydroxy-2,7-dimethoxy xanthone, 1,2-dihydroxy-6,8-dimethoxy xanthone, 1-hydroxy-3,7,8-trimethoxy xanthone, which exhibited antimalarial activity against Plasmodium berghei infections[46].

Quantitative determination of the major component andrographolide by HPLC analysis:

The amount of andrographolide present in the plant was quantified before and after the maturity stages by HPLC using methanol:water (65:35) as mobile phase, at a flow rate of 1.5 mL/min[47]. The analysis revealed maximum andrographolide content in post-flowering stage than immature plant. Further the study suggested that the medicinal effects of *A. paniculata* depend on the environmental factors such as climate, habitat and also on its constituents.

Pharmacological properties

A. paniculata and the diterpenoids are the main constituents in traditional indigeneous medicine to treat various liver disorders such as hepatitis[48,49] or damage induced by galactosamine[50] paracetamol[51] and carbon tetrachloride[52,53]. The choleretic potential of the major diterpenoids as a stimulant for proper functioning of gall bladder in anesthetized guinea pigs and conscious rats was reported by Shukla et al. in 1992[54]. The efficacy of andrographolide and neoandrographolide against ethanol and acetaminophen induced liver damage was comparable to silymarin[55]. However previous studies were carried out in this area suggested[56], besides andrographolide several other constituents in the extract may be responsible for the hepatoprotective activity of the plant. The plant extract and its main active constituents diterpenoids were investigated for its influence on liver metabolizing enzyme such as cytochrome P450, glutathione S-transferase etc[57,58]. The alcohol and aqueous extract are found to increase CYP1A1 and CYP2B without altering the P450 and inhibit CYP1A2 and CYP2C in rat and human liver chromosomes[59,60]. Further clinical research is recommended to draw conclusion on the effect of the *A. paniculata* and its constituents on hepatic metabolizing enzymes.

Aqueous extract of *A.paniculata* were investigated for their radical scavenging and antioxidant activity in brain and liver organs of animal models and the observed activities were summarized due to the presence of flavonoids in the extract[61-63]. The methanol extract of the plant was also found to be effective in scavenging reactive oxygen species (ROS˙) and LPS- stimulated nitric oxide (NO˙) radicals[64-66]. Intake of *A. paniculata* extract help to maintain the balance of nitric oxide/endothelin in the tissues[67], increase blood clotting duration; decreasing arterial narrowing due to injury or high fat diet, heart muscle damage after myocardial infraction in animals[68,69], activate fibrinolysis and antihypertensive effects. Hence plant extracts can be administered in pre- and post-treatments in angioplasty. Thisoda et al., in 2006 suggested that the major diterpenoid andrographolide and 14-deoxy-11,12-didehydroandrographolide (DDA) in the aqueous of the plant are mainly contributing to antiplatelet aggregation[70].

A. paniculata was found to be used in traditional medicines for lowering fever. The chief phytochemical constituent, andrographolide reported to possess antipyretic, antiulcerogenic and analgesics activity which is comparable to that of aspirin[71,72]. Different mechanisms have been proposed on anti-inflammatory activity of andrographolide involving modulating macrophage and neutrophil activity. Studies throw light on the exploring the potential of the plant and the diterpenoid in treating neurodegenerative disease such as Parkinson's disease[73,74]. Formulations containing andrographolide and neoandrographolide were reported to be effective against bacillary dysentery and diarrhea compared to standard drugs chloramphinicol/furazolidine[75]. Several reports on *A. paniculata* extract and in combination with Eleutherococcus senticosus in treating uncomplicated upper respiratory tract infections (UTRI) in adults and children in the age group 4-11 yrs are available[76-80]. However more clinical trials should be performed on *A. paniculata* to test its efficacy in UTRI as the results on combinations with *E. senticosus* was reported to be

effective. Oral inake of *A. paniculata* plant as well as the standardized dried extract of *A. paniculata* (SHA-10) efficiency was comparable to acetaminophen in relieving symptoms from pharyngotonsillitis[76].

The potential of *A. paniculata* in treating cancer, HIV infections were largely explored[81,82,83]. Andrographolide also reported to possess anticancer and immune stimulating potential[84,85,1]. The plant extract as well as the andrographolide were reported to induce myeloid leukemia cell differentiation in mice[86].

Hypoglycemic studies on *A. paniculata* administered to non-diabetic rabbits reported that the aqueous extract was effective in reducing hyperglycemia in oral glucose fed rabbits and the plasma glucose levels in streptozotocin induced diabetic rats in dose dependent manner but not in adrenaline injected animals[87]. Studies on water and alcohol extract of *A. paniculata* proposed several mechanistic way for explaining the hypoglycemic activity but still further work needed for identifying the active constituents[88,89]. The crude aqueous extract is found to possess antimicrobial activity some strains such as S. aureus, P.aeruginosa but no significant activity against *E.coli, Salmonella, Staphylococcus aureus*[90,91,92]. Antimalarial potential of *A. paniculata* against Plasmodium berghei and Plasmodium falciparum were attributed to reactivation of superoxide dismutase, an antioxidant enzyme in the former and presence of xanthones in the extracts in the latter species[93,94,95]. Xanthones from the plant are also reported to possess protozoa growth inhibitory potential[96]. *A. paniculata* and its phytochemicals are active constituents in formulations to treat snake venom[75] and filariasis[97]. Efficacy of *A. paniculata* extract as central nervous system depressant drugs has been proved in 2001[98].

Mechanism of anticancer effects

Ethanol extract of *A. paniculata* showed the potential anti cancer activity on a range of cancer cells like Jurkat (lymphocytic), PC-3 (prostate), HepG2 (hepatoma) and Colon 205 (colonic) cells[99]. Andrographolide and its analogues have also showed similar effects against human leukemia HL-60 cells. They exert direct anti cancer activities on cancer cells by cell-cycle arrest at G0/G1 phase through induction of cell cycle inhibitory protein and decreased expression of cyclin dependent kinase[100,85]. Angrographolide also induces apoptosis in human cancer cells via the activation of capase 8, release of cytochrome C from mitochondria and activation of capase cascade and/or via the activation of tumor suppressor p53 by ROS dependent c-Jun NH_2-terminal kinase (JNK) activation, thereby increasing p53 phosphorylation and protein stabilization[101,102].

The anti cancer effect may also contributed by the enhancement of immunity, inhibition of angiogenesis and tumor cell migration. Extracts of *A. paniculata* inhibiting human cancer cell growth by enhances proliferation and IL-2 induction in human peripheral blood lymphocytes [103].

Studies also revealed that ethanol extract of the plant and andrographolide stimulated the cytotoxis T lymphocytes (CTL) activity through enhanced release of IL-2 and IFNγ in serum thereby inhibiting tumor growth[64]. Andrographolide inhibit angiogenesis for tumor metastasis via down-regulating matrix metal loproteinases-7 (MMP-7) expression, possibly by inactivating protein-1 (AP-1) through suppressing P13K/Akt signaling pathway[104,105]. The results of these researches suggest the therapeutic strategy of *A. paniculata* and andrographolide in combination with chemotherapeutic agents to treat cancer.

Toxicity

Traditional medicines such as Ayurveda advocates avoiding the consumption of the plant during pregnancy. Studies on antifertility effects of *A. paniculata* and its main constituent, andrographolide in animal models revealed the antispermatogenic and ovulation hindering effects[106,107]. Most of the trials were carried out for a short duration. On the basis of these facts extensive research to optimize the concentration for clinical feasibility is now greatly demanded. So the choice of *A. paniculata* as an alternative resource in medical therapy requires further active research involving the isolation of its phytoconstituents and longer clinical trials.

CONCLUSION

The major bioactive compound 2' oxygenated flavonoids which occur rarely in nature, in addition to andrographolide diterpenoids from *A. paniculata* confined the chemotaxonomic importance of *Andrographis* species in the *Acanthaceae* family. In traditional Chinese Medicine the pretreatment with various extracts and constituents of *A. paniculata* against hepatotoxicity are very consistent. The plant is found to be very effective in a number of polyherbal formulations for the treatment of liver ailments. Andrographolide, the primary medical component of *A. paniculata* in terms of bioactive properties and abundance has been reported for its anticancer and anti HIV effects leads to explore the relevance of plant in modern medicine as a potent chemotherapeutic agent. Neoandrographolide another active component of *A. paniculata* has also been reported to show anti HIV activity. The ent-labdane diterpenoids reported from the species are exhibited significant antimicrobial effect. Among the andrographolide analogues, 14-deoxy-11,12-didehydro andrographolide is immunostimulatory, antiinfectve and antiatherosclerotic and 14-deoxy- andrographolide is immunomodulatory and antiatherosclerotic. Among the less abundant constituents of the plant andrograpanin and isoandrographolide are anti-inflammatory and tumor suppressive.

Although the results from this review are very promising for the use of the plant as a multi-purpose medicinal agent, several limitations currently exist in the current literatures. While Kalmegh has been used successfully in

Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use.

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