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Review Article

A Prospective Review on Phyto-Pharmacological Aspects of *Andrographis paniculata*

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ABSTRACT

Andrographis paniculata Nees is an annual herbaceous plant which belongs to the family Acanthaceae. It is commonly known as Kalmegh, is found in the plains of India, China, Pakistan, Sri Lanka and South Asia and is native to India and Sri Lanka. Kalmegh is known to be the "king of bitters" though it is of small size and it also has a similar appearance and taste as that of the Neem plant. It is one of the widely used effective medicinal plants in the world. All parts of this plant are used to extract the potential phytochemical, but the composition of phytoconstituents mostly differs from one part to another in a season, place and time of harvest. It is a traditional medicinal plant widely used in the treatment of anti-inflammatory, anti-bacterial, anti-oxidant, hepatoprotective, hematocidal, anti-HIV, anti-cancer, anti-diabetic, arthritis, rheumatism, cough, cold, multiple sclerosis, depression, diarrhoea, dysentery, candida, fevers, herpes, leprosy, malaria, jaundice, tuberculosis and several infectious diseases ranging from malaria to dysentery. The plant is widely used in Ayurvedic and homeopathic system of medicine. The medicinal value of this plant is due to the active ingredients via andrographolide and neoandrographolide, which are derivative of diterpinoids. It prevents oxidative damage and inhibits binding of toxic metabolite to DNA.

Key words: *Andrographis paniculata,* Anthraceae, Andrographolide, Neoandrographolide, Kalmegh.

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INTRODUCTION

Nature is a rich source of medicinal agents, since the beginning of mankind.[1] In Ayurvedic medicine, there are a number of herbs, which have been used traditionally for treating an enormous variety of ailments. Herbal plants are the richest bio-resource on drugs of the ancient system of medicine Nutraceuticals, modern medicines, folk medicines, pharmaceutical intermediates, chemical entities and also food supplements.[2]

Andrographis paniculata

A. paniculata Nees (Acanthacae), commonly known as king of bitter, is a perennial herb widely cultivated in India, China, South Asia, South Africa, Pakistan and Sri Lanka. *A. Paniculata* or Kalmegh is one of the enormous herbs used in various Ayurvedic formulations,[3] where it is used to treat infections and some diseases, while being used before antibiotics were created. Mostly, the leaves and roots were used for medicinal purpose.

A. paniculata, the Kalmega of Ayurveda, is a bristling annual herb eminently bitter in taste in each and every part of the plant body. The plant is known as maha-tita literally "king of bitters" in North Eastern India and known by several vernacular names. It is also known as "Bhui-neem".

The plant is much smaller in size, exhibits identical appearance and has bitter taste of neem (*Azardirachta indica*). The genus Andrographis consists of 28 species of small annual shrubs basically distributed in tropical Asia. Only a few species are medicinal of which *A. paniculata* is the most popular.[4]

Distribution

A. paniculata is distributed in tropical Asian countries frequently in isolated patches. It can be found in various habitative plains, hill slopes, waste lands farms, dry or wetlands, seashore and also road sides. Native population of *A. paniculata* is distributed all over south India and Sri Lanka which may constitute to the origin centre and diversity of species. The herb is also available in northern states of India, Malaysia, Indonesia, West Indies and America. In India, it is probably found in the plains and hilly areas up to 500 m, which accounts for its extensive use. For years, immemorial villages and ethnic communities in India have been using this herb for treating different types of ailments.

Taxonomic hierarchy

Kingdom: Plantae
Division: Angiospermae
Class: Dicotyledoneae
Order: Tubittorae
Family: Anthraceae
Genus: *Andrographis*
Species: *paniculata* Nees

Morphology

A. paniculata is an annual, branched, erect plant running ½ to 1 m long in height as shown in the Figure 1. The leaves of *A. paniculata* are dark in color, simple, opposite, lanceolate, glabrous2- to 12-cm-long, 1- to 3-cm-wide acute apex; entire margin flower consists of small linear 5-particle calyx and tube narrows to about 6-mm-long white corolla with violet marking. Two stamens inserted in the throat and two called as superior ovary. 1- to 2-cm-long, 2.5-mm-wide, linear-ablong, compressed erected capsule.[5]

Phytoconstituents

A. paniculata contains diterpenes, lactones and flavonoids. Flavonoids mainly endure in the root and also have been isolated from the leaves. The aerial parts contain alkanes, ketones and aldehydes. Although, it was initially known that the bitter substance in the leaves was the lac-

tone andrographolide, later investigation showed that the leaves contained two bitter principles-andrographolide and a compound named kalmegin four lactoneschuanxinlian. A (deoxyandrographolide), B (andrographolide), C (neoandrographolide) and D (14-deoxy-11,12dihydroandrographolides) were isolated from the aerial parts in China.[6] Diterpene glucoside (deoxyandrographolide 19 beta-D-glucoside) has been detected in the leaves,[7] and six diterpenoids of the ent-labdane type two diterpenes, glucosides and four diterpene dimmers (bis-andrographolides A, B, C and D) have been isolated from aerial parts.[8] Two flavonoids identified as 5,7,2′,3′-tetramethoxyflavonone and 5-hydroxy-7,2′,3′- trimethoxyflavonone were isolated from the whole plant[9] while from the aerial parts, 14 diterpenoids and 12 new flavonoids have been reported.[10] Two new flavonoids glycosides and new diterpenoids (andrographic acids) were recently reported[11] and two new ent-labdane diterpenoids glycosides were isolated from the aerial parts[12] (Table 1).

Figure 1: Image of the plant Andrographis paniculata.

PHARMACOLOGICAL ACTIVITIES

Hepatoprotective activity

A. paniculata is used copiously in the traditional system of Indian medicine as a hepatoprotective and hepatosimulative agent.[22] A very few studies on the effect of crude extract of *A. paniculata* on liver function are available. Most studies for hepatic effects have been led on either andrographolide or other supposedly active principles.

Andrographolide, a diterpinoid lactone, was isolated from *A. paniculata*. Anti-hepato toxic activity of andrographolide was compared with methonol extract and of the andrographolide-free methonol extract of the plant, using CCl_4 (Carbon Tetrachloride) -intoxicated rat. Biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum bilurubin and hepatic triglycerides were estimated. The increase in five biochemical parameters was found to be 48.6, 32 and 15 %, which was induced by overall inhibition of CCl_4. Andrographolide (100 mg/kg) was found to be normal. Completely, their CCl_4 induced increase in the pentobarbitone-induced sleep time in mice. The result suggested that andrographolide is the major active anti-hepatotoxic principle present in the *A. paniculata*, which has been reported by Handa and Sharma.[23]

The significant chloretic effect of andrographolide is found in conscious rats and anaesthetized guinea pigs. The protection of andrographolide against acetaminophin-induced reaction in volume and contents of bile was better that that produced by silymarin, which was reported by Shukkla *et al*.[24] Multiple-dose pretreatment with arabinogalactan proteins and andrographolide was protective against ethanol-induced hepatotoxicity in mice and was deemed comparable to the efficacy of silymarin.[25]

Kapil and Koul[26] reported that the CCl_4-induced increase in pentabarbitone-induced sleep time in mice is also completely normalized by andrographolide. The intraperitoneal pretreatment for three consecutive days with andrographolide on CCl_4-other butyl hydroperoxide-induced hepatotoxicity in mice was compared with diterpense-andrographiside and neoandrographolide. Both compounds showed a greater protective effect than andrographolide comparable to silymarin and neoandrographolide-normalized glutathione levels.

Table 1: Reported chemical constsituents and bioactives of *Andrographis paniculata*.

S. no	Reported chemical constituents	Pharmacological actions	References
1.	Andrograhpolide	Anti-cancer, hepatoprotective	14, 15
2.	14-deoxy andrographolide	Enhanced proliferation and interleukin-2 induced in human peripheral blood lymphocide	16
3.	14-deoxy-11,12-didehydro andrographolide	Anti-cancer	16
4.	14-deoxy-11-oxo andrographolide	Anti-lesminasis and anti-parasitic diseases	17
5.	Neo andrographolide	Anti-inflammatory	18
6.	Andrographolide	Liven cleansing and hepatitis	19
7.	Kalmeghin	Fever and cold	20
8.	Andrographisid	Anti-oxidant, anti-lipo pero oxidant carcinogenic detoxification	21, 22

Antioxidant activity

Antioxidant activity and its constituents of *A. paniculata* have been illustrated by various investigators. Oja and Nandava[27] reported that the hydro alcoholic extract of *A. paniculata* prevented isoproterenol-induced evaluated lipid peroxidation and anti-oxidant enzymes activity viz. superoxide dismutase (SOD), catalase (CAT), glutathione perioxidase (GPX) and levels of reduced glutathione level in heart. In addition, the extract also prevented leakage of *lactate dehydrogenase* (LDH) from the heart and rescued it from isoproterenol-induced myocardial ischaemic injury. The study indicated the anti-oxidant activity of *A. paniculata* and justified its use in heart disease.

Administration of *A. paniculata* prior to diclofenac significantly declines the hepatic anti-oxidant status, i.e., SOD, CAT, GPX, *Glutathione* S-transferases (GST) and glutathione were increased in the *A. paniculata* plus diclofenac-treated group than in the diclone-treated group. So the result of the Soumendra *et al*.[28] the study concluded that the aqueous ethanol extract of the *A. paniculata* against diclofenac-induced acute toxicity is mediated either by preventing the refuse of hepatic anti-oxidant status or to its direct radical scavenging capacity. Das *et al*.[29] reported the nicotin-induced inhibition of mitochondrial electron chain complexes and the resultant increase in nitric oxide (NO) in different parts of rat's brain prevented by simultaneous treatment with the aqueous and ethanol extracts of *A. paniculata*. The aqueous extract exhibited the greater anti-oxidant activity. Andrographolide pretreatment significantly attenuates accumulation of phorbol-12-myristate-13-acetate (PMA)-induced formation of ROS and N-formyl-methionyl-leucyl-

phenylaline (fMLP)-induced adhesion and transmigration of ROS and fMLP-induced adhesion and transmigration of peripheral human neutrophilis was only partially reversed by andrographolide. This study suggested that the prevention of ROS production was partly mediated by the direct actuation of protein kinase by PMA and partly mediated by down-regulation of surface MAC-1 expression, an essential integrin for neutrophil adhesion and transmigration, respectively.[30]

Excessive amounts of NO and prostaglandin E_2 (PGE_2) due to expression of inducible isoforms of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) from activated macrophages play a significant role in inflammatory process. Lipopolysaccharides (LPS) stimulates and promotes secretion of pro-inflammatory cytokines from macrophages and causes induction of iNOS, resulting in increased production of NO.[31] Incubation of macrophages with methanol extract, andrographolide and neoandrographolide inhibits LPS-stimulated NO production in a concentration-dependent manner.[32] Andrographolide incubated LPS-induced increase in tumour necrosis factor-alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor.[33] Neoandrographolide also inhibits PGE_2 synthesis[34] and TNF-α in LPS-stimulated macrophages and its oral administration of mice significantly suppresses dimethylbenzene-induced ear edema acetic acid-induced vascular permeability. APIO134, a refined extract of *A. paniculata*, also significantly reduces activities of lipid peroxide and endothelin, while the activities of NO, cGMP and SOD are significantly enhanced in experimental atherosclerotic rabbits.[35]

Anticancer activity

A. paniculata is a traditional plant which contributes towards its various biological activities, including anti-cancer property. Hsieh *et al.*[36] reported that dehydroandrographolide induced autophagy in human oral cancer cells by modulation p53 expression, activating JNK ½ and inhibiting AKT and p38; an administration of dehydroandrographolide effectively suppressed the tumour formation in the oral carcinoma xenograft. This is the first study to reveal the novel function of dehydroandrographolide in activating autophagy, suggesting that dehydroandrographolide could serve as a new and potential chemopreventive agent for treating human oral cancer.

The radiosensitizing effect of andrographolide in human ovarian SKOV3 xenograft examined the molecular mechanism of andrographolide-mediated radiosensitization. Nude mice bearing human ovarian SKOV3 were treated with andrographolide to investigate the effect of drug administration to tumour growth, radiosensitivity, apoptosis and autophagy. The result correlated with an increase with Bax/Bcl-2 protein ratio and p-p53 expression after exposure to combination treatment. The level of beclin and Atg5 and the conversion from LC3-I to LC3-II, three important proteins involved in autophagy, were increased. In *in vivo* method, andrographolide acts as a powerful radiosensitizer in human ovarian SKOV3 xenografts and it promotes the Bax/Bcl-2 protein ratio. The activation of caspase-3 leads to enhanced apoptosis as well as autophagy.[37]

Andrographolide has been reported to have anti-cancer activity in various types of cancer due to its capacity to inactivate the NF-kB pathway. Andrographolide significantly inhibits the proliferation and invasion of Npc cells. The work provides the evidence that the NF-kB pathway is the potential therapeutic target and may also be indispensable in the auto-mediated anti-cancer activities in nasopharyngeal carcinoma.[38]
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Zhang *et al.*[39] reported that hypoxia-induced factor-1 (HIF-1) is a master regulator of the transcriptional response to hypoxia. HIF-1α is one of the most compelling anti-cancer targets. Andrographolide was newly identified to inhibit HIF-1 in T47D cells by a dual-lucitarase reports assay. Andrographolide inhibited T47D and MDA-MB-231 cell proliferation and colony formation. The results highlighted the potential effects of andrographolide, which inhibits HIF-I and hence, many developed as an anti-tumour agent for breast cancer therapy in the future.

Andrographolide inhibited hepatoma tumour growth *in vivo* and it decreased VEGFD m-RNA and pth expression in hepatoma Hep3B and HepG2 cells. It decreased cFOS pth expression and its translocation into nucleus and also reduced AP-1 luciterase activity. Andrographolide-induced proliferation of cFOS proteosome inhibits MG132 reversed the decreased expression cFOS pth and the decreased m-RNA and pth expression of VEGFD. SP600125, an inhibitor of C-Jun N-terminal kinase (JNK), reversed the decreased expression of cFOS and VEGFD induced by andrographolide.[40]

Antidiabetic activity

A. paniculata nees were used for several purposes mainly for treatment of diabetes mellitus. The study evaluated andrographolide for its paniculatic effect in neonatal streptozotoion-induced diabetic rats. Andrographolide significantly decreased the levels of blood glucose and improved diabetic rat islet and beta cells. A**ndrographolide**-enriched extract of *A. paniculata* (AEEAP) exhibited modulate hypoglycaemic effect on the blood glucose level. Moderate changes in beta cells were observed after AEEAP treatment. They could restore decreasing pancreatic insulin content.[41]

Zhang *et al.*[42] reported the protective effect of andrographolide in the development of autoimmune diabetes. Randomly divided four groups of NOD mice were administrated with water and andrographolide at 50, 100 and 150 mg/kg body weight for 4 weeks. Oral glucose tolerance and histopathological insulates were examined. Th1/Th2/Th17 cytokin secretion was determined by ELISA. The transcriptional profits of T-bet, GATA3 and RORγt in the pancreatic lymphatic nude samples derived from the NOD mice were detected by RT-PCR. This protective status correlated with the substantially decreased protection of interferon (IFN)-γ and interleukin (IL)-2 increased IL-10 and transforming growth factor (TGF)-β and α refused IL-17. Andrographolide also increased GATA3 m-RNA expression and decreased T-bet and RORγt m-RNA expressions. The results suggest that andrographolide prevented type I diabetes by maintaining Th1/Th2/Th17 heamostasis.

Chaursk *et al.*[43] reported the anti-diabetic potential chloroform fraction of the ethanol effect of *A. paniculata* and diabetes laden gene expression alteration. Streptozotosion (60 mg/kg) induced type two diabetes albino mice. Fasting blood oral glucose tolerance serum liquid profile, tissue glucose in content, glucosys-phosphatase and hexokinase enzymes level in liver *in vitro* and *in vivo* insulin estimation were measured on last date of treatment. Biochemical enzymes such as glucose-6- phosphatase and hexokinases were evaluated in body tissues. Apart from this *in vitro* and *in vivo* insulin estimation, diabetogenic gene expression analysis of GK, PEPCK, G-6 phase, Gluf-4 AR, PPAR-αγ and TNF-α was evaluated using the RT-PCR technique. Anti-diabetic screening of fraction of *A. paniculata* at molecular level revealed significant anti-diabetic activity.

Infectious diseases

Andrographolide is found to be active against pulmonary types of tuberculosis, tuberculosis meningitis and acute pyelonephritis. Intra-arterial or retrogate intravenous injection of the herb was effective in thrombogritis obliferansis especially of "heat toxic type". Ten cases of viper bites were reported to be cured within 3–5 days by a compound which contains *A. paniculata* . A phase I, dose-intense clinical trial of andrographolide was conducted on 13 HIV-positive patients and five HIV-negative healthy volunteers. The administration of andrographolide to HIV-positive patients significantly increased the baseline

mean of CD4+ lymphocyte count from 405 to 501 cells/mm^3. There were no significant changes in plasma HIV-1 RNA levels. *A. paniculata* has also been used for uncomplicated upper respiratory tract infections (URTIs).[44]

CONCLUSION

Andrographolide, main active constituent of *A. paniculata*, is a diterpenoid lactone having a variety of pharmacological effects specified in Ayurveda, Unani, Sidhha and Chinese medicine system. This herb has been venerated for treating infectious diseases and highly regarded as having preventative effects against ailments such as liver damage, hyperglycaemia, dysentery, cancer, pulmonary, tuberculosis, AIDS, acute and common cold, flu, myocardial infarction, inflammation and blood clotting. Therefore, further research may be undertaken to develop potent formulations consisting of *A. paniculata* and its isolated molecule, andrographolide, by making use of novel herbal drug delivery system, such as microparticles, vesicular system or through complexation with lipid or other suitable novel carrier.

ABBREVIATIONS

HIF-1: Hypoxia-induced factor-1; **HIV:** Human immunodeficiency virus; **IFN:** Interferon; **IL:** Interleukin; **iNOS:** isoforms of Nitric Oxide Synthase; **JNK:** C-Jun N-terminal kinase; **LDH:** Lactate Dehydrogenase; **LPS:** Lipopolysaccharides ; **NO:** Nitric oxide; **PGE2:** Prostaglandin E2; **PMA:** Phorbol-12-myristate-13-acetate; **SOD:** Superoxide Dismutase; **TNF-α:** Tumour Necrosis Factor-alpha; **URTIs:** Upper respiratory tract infections.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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