

***Andrographis paniculata* (Burm.f.) Wall. ex Nees. - A potent herb with immense pharmacological potential**

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ABSTRACT

Medicinal plants, as autochthonous sources of medications, have been utilized since primeval times. *Andrographis paniculata* (AP) is considered one of the most potent herbs around the world. Otherwise known as Kalmegh, the herb has traditionally been used as a cure for the common cold, diarrhoea, jaundice, and fever owing to numerous causes. Apart from this, the herbal parts can act as liver intoxicants as well as cardiovascular (CVD) vigor and are also considered to possess free radical scavenging activity. Habitation, season, and harvesting time of the crop have an effect on phytochemical composition that extensively differ from one part to another. In this review, we discussed the ethnobotany of this plant briefly. Apart from these various pharmacological activities with a specific focus on anticancer properties of the herb are also proposed.

Keywords: *Andrographis paniculata* (AP), andrographolide, anticancer, ethnopharmacology, pharmacological potential.

INTRODUCTION

Andrographis paniculata (Burm.f.) Wall. ex Nees., belongs to the Acanthaceae Family- is an annual herbaceous plant and is generally cultivated in Southern Asia, China, and parts of Europe. The herb is usually renowned as kalmegh, bhumineeb, and chirayata. It is a valued traditional medicinal plant and has its usage in the Unani and Ayurvedic medicine systems (Chopra *et al.*, 1956). The herb is commonly used to normalize body heat, dissipate toxic materials from the body; preclude common cold, infections of the upper respiratory tract as well as sinusitis and fever (Gabrielian *et al.*, 2002). It also acts as an antidote against snakes and insects' venom (Samy *et al.*, 2008). Phytochemical screening of various organic solvent extracts of AP plant parts, such as leaves and bark of the stem exhibited the availability of glycosides, phytosterol, saponins, tannins, flavonoids, and terpenoids. Terpenoids are considered to be the crucial constituents in the leaves as well as stem barks (Pandey *et al.*, 2019). The occurrence of vital phytochemicals in AP makes the plant valuable for

treating altered ailments and has the potential of providing useful drugs for human use (Pandey *et al.*, 2019). This paper will provide a deep insight into the ethnobotany, a few agronomic techniques, a depiction of the potent chemical components, and the pharmacokinetics of Kalmegh. Furthermore, chemical possessions, biological roles, and their probable modes of action are also to be considered.

The plant has been reported to unveil several means of biological activities *in vivo* as well as *in vitro* such as, anticancer (Iruetagoiena *et al.*, 2005; Li *et al.*, 2007), anti-inflammatory (Wen *et al.*, 2010), immunomodulating/ immunostimulatory (Calabrese *et al.*, 2000), antihyperglycemic, antihyperlipidemic, hepatoprotective, cardiovascular, antiviral (Wiert *et al.*, 2005), antimalarial and filaricidal, antidiarrheal, antibacterial (Singha *et al.*, 2003; Mishra *et al.*, 2009). The distinctive secondary metabolites encountered in this herb have substantially enriched its eminence in the arena of medicinal herbs. The quantitative determination of pharmacognostic parameters will facilitate in setting standards for crude drugs (Sharma *et al.*, 2012).

Vernacular names

The herb is famous in diverse local languages in several parts of the world. In Hindi, the herb is famous as Kalmegh, Kiryat, and Mahatit. The herb is well known as Kiriyata and Olikiriyat in Gujrati. In Malyalam, it is called as Nilaveppu, Kiriyatta. Whereas NelaVemu and Nilavempui are the common names in Telugu and Tamil respectively. Bhuinimb, Kirata, and Mahateet are the local names in Sanskrit. English: Creat, Green Chirayta, King of bitters (Verma *et al.*, 2019).

Origin

Kalmegh is an inhabitant of Taiwan, India, and Chinese province. The herb is usually located in Asia's tropical and warm temperate evergreen forests. The mainland of Southeast Asia (the Caribbean islands, Indonesia, Malaysia) and Sri Lanka, are the other continents, where the herb can be easily found. This plant is also found in altered geographical conditions of America, the West Indies, and Christmas Island (Verma *et al.*, 2019).

Geographical distribution

The species is native to tropical South-East Asia and have its presence throughout warmer parts of India. The species is scattered in tropical Asian realms, frequently in remote areas. The herb can be sited in an array of habitations, for instance, plains, hillsides, coastlines, and disturbed and cultivated areas (roadsides and farms) (Niranjan *et al.*, 2010; Mishra *et al.*, 2007). Native populations of AP extend throughout south India and Sri Lanka which conceivably exemplify the epicenter of origin and diversity among species. The herb is an introduced species in northern parts of India, Java, Malaysia, Indonesia, the West Indies, and elsewhere in the Americas. The species also occurs in the Philippines, Hong Kong, Thailand, Brunei, Singapore, and other parts of Asia, where it may or may not be native (Perumal Samy *et al.*, 2017). Contrasting other species of the genus, *A. paniculata* is of prevalent occurrence in most places in India, together with the plains and hilly areas up to an elevation of 500 m (1,600 ft). In India, the principal source of plants is collected from its wild habitat. According to the IUCN database, the plant is regarded as Low Risk or of Least Concern (Gowthami *et al.*, 2021).

Climate and soil

The herb is a hardy species in tropical and subtropical regions and therefore thrives well in almost all types of soil. However, soils relatively superior in heavy metals such as Al, Cu, and Zn are preferred for the crop. Medium productive sandy loam to clay-loam soils with a pH range of 6.5 -8.5 is ideal for the cultivation of the crop. Though it is cultivated in open fields still can withstand partial shade of trees (Verma *et al.*, 2019).

Propagation and nursery aspect

Both seed and vegetative methods can be utilized for raising the herb. However, propagation through seed is easy and economical when the cultivation is of commercial importance. Towards the beginning of September seeds of the herb have been sown in nursery beds, after soaking in water. About 650-750 g of seeds is the requisite for raising a nursery for one hectare of land (Verma *et al.*, 2019). Seeds are usually sown in nursery beds prepared by taking a mixture of normal soil, sand, and organic matter in a ratio of 1:1:1 and at a spacing of 5 cm in rows. It takes around 8-10 days for germination to commence. The direct sown crop is scattered thinly with a seed proportion of 1.5 kg per hectare (Verma *et al.*, 2019).

Agronomic techniques

Plants of Kalmegh traditionally grow through seed culture. The recommended time for sowing is usually from May to July. However, seed latency is a foremost limitation in the commercial farming of AP. Application of phytohormones and treatment with hot water has been recommended, to prevail over this problem (Kumar *et al.*, 2011). The technique is not adequate as per the commercial measures concerned due to inconsistency amongst the scions derived from seeds and the deferred root system of seedlings (Martin *et al.*, 2004). Numerous non-traditional proliferation approaches, for instance, micropropagation techniques are therefore the alternatives to generate huge amounts of saplings in a small duration, as well as to improve phytochemical contents in AP (Vijaylaxmi and Murthy, 2012). The yield of the herb is influenced by planting and time of harvesting (Nemade *et al.*, 2003).

Land preparation and fertilizer application

The land should be organized well by frequent ploughing to make the soil pounded. Organic manure at a rate of 20 t ha⁻¹ is applied as a basal application. An NPK fertilizer at a proportion of 75:75:50 kg ha⁻¹ should be given in two split doses. The first dose is at the planting stage, followed by the second; that is 40 days after plantation. The employ of Azospirillum (5 kg) along with Phosphobacteria (5 kg) ha⁻¹ will give satisfactory results.

Transplanting and optimum spacing

The nursery-raised seedlings are transplanted in the main field, upon reaching 10-25cm with an optimum distance of 30 x30 cm from plant to plant and row to row (Ram *et al.*, 2008; Kanjilal *et al.*, 2002).

Irrigation and weeding

Light irrigation as per prerequisite can be provided at regular intervals to aid the early establishment of seedlings, once the transplantation has been done. There is no need for additional irrigation as the crop is transplanted in the season of monsoon. Whenever there is a requirement for water, the field can be irrigated at intervals of 20-25 days (Verma *et al.*, 2019).

Kalmegh is a short-duration crop and is cultivated in the *Kharif* season. Thus, weed invasion is an immense issue that deteriorates the quality and quantity of herbs. Since it is an herbaceous plant, the field should be free from weeds. Two to three weeding, usually one after 20 days and another after 60 days of plantation are essential during the crop season. The appliance of the herbicide pendimethalin at the rate of 1 kg ha⁻¹ as pre-emergence followed by quizalofop ethyl at the rate of 50 g per hectare as post-emergence was found to be an efficient weed control agent. This should be followed by one mechanical weeding for accomplishing high biomass yield (Meena *et al.*, 2017; Semwal *et al.*, 2016). There were no major insect pests or disease infestation has been recorded in Kalmegh. Brown Scale, *Parasaisettia nigra*, was found to causing considerable damage, with the affected plants showing stunted growth and drying. Semilooper, *Panilla albopenstata* dented the plants by feeding on young leaves, flower buds, and tender

Pods (Rani and Sridhar, 2005). Application of Azadirachtin (1-2%) leaf extract upon the herb was found to be helpful (Suganthi and Sakthivel, 2013).

Crop maturity and harvesting

Generally, the crop matures after 120 days of sowing in October and November. Most pods mature fully in January and February (Verma *et al.*, 2019). The planting and harvesting period influences the yield and quality of the crop. The active principle of the plant varies with time intervals and diverse environmental conditions (Kumar *et al.*, 2002). It is harvested when most plants are in bloom. Upon maturity, the plants should be uprooted leaving few healthy plants in the field for seed production. The fruits once mature, should be picked up and dried in the sun for seed collection (Wankhade *et al.*, 2005).

Postharvest management and storage

After uprooting the plant, it should be sun-dried for two days followed by shade drying. Once dried, the materials were packed in gunny bags and stored in dark, airy, and moisture-free places. The crops harvested after three months of cultivation showed the utmost sum of andrographolide, a foremost bioactive compound of AP followed by that just beforehand the flowering period (Tipakorn, 2002).

Yield and cost of cultivation

Most of the States of India have been reported for the commercial cultivation of Kalmegh, with an average yield (as a whole plant) of 2.5 t ha⁻¹. The approximate cost of the crop for one hectare comes to around INR 25,000/-.

Trade

Under the trade appellation Kalmegh, on normal 2,200-5,500 t of the herbage is traded in India.

Phytochemistry (chemical constituents)

Andrographolide (AD) is one of the foremost compound among the active principles that were extracted from the leaves and roots of Kalmegh. The compound is highest in the leaves; where as seeds have the lowest possible content (Sharma *et al.*, 1992). Diterpenoids such as deoxy and rographolide-19-β-D-glucoside and neo-and rographolide are two of the bitter components that have been isolated from the leaves (Weiming and

Xiaotion, 1982). The roots were found to be rich in apigenin-7, 4'-di-O-methyl ether, andrographolide, and a novel natural flavone, 5-hydroxy-7, 8, 2', 3'-tetramethoxy flavone (C₁₉H₁₈O₇). Andrographolide D (14-deoxy-11, 12-didehydroandrographolide), homoandrographolide, and andrographan, andrographon, andrographosterin and stigmaterol are the other components reported in the herb (Siripong *et al.*, 1992). Flavonoids, comprising 5, 7, 2', 3'-tetramethoxyflavanone, along with other flavonoids, andrographolide diterpenoids, and polyphenols, were acquired from the entire plant (Koteswara Rao *et al.*, 2004). The above said phytoconstituents are considered to be accountable for various pharmacological activities of the herb.

Pharmacological potential (medicinal properties)

According to Ayurveda the herb "Kalmegh" is astringent, pungent, cooling, laxative, wound healing (vulnerary), antipyretic, antiperiodic, anti-inflammatory, expectorant (Mucoactive agents), depurative, sleep-inducing (soporific), anthelmintic, digestive, and stomachic. The herb is a valuable agent against hyperdispsia, burning sensation, ulcers, fevers, skin diseases, leprosy, colic, flatulence, diarrhoea, dysentery, and haemorrhoids, etc. (Mall and Tripathi, 2016). Kalmegh is also renowned as an apparent Homoeopathic drug. Fresh leaves of the herb are used to prepare "Alui", a well-known household medicine in Bengal (India), and are given to children suffering from stomach complaints. It has also been proven to be a hepatoprotective drug. Blocking of the voltage-operated calcium channels as well as inhibition of Ca (+2) influx by the dried herbal extract induces relaxation of the uterus (Hancke *et al.*, 1995). Initial studies in animals ascertained that AP might help cure cardiac disease (Zhao, and Fang, 1991; Zhang, and Tan, 1997). It appears to stimulate gallbladder contraction, as well as prevent blood clots (Varies, 1993). The herb also showed certain other phytochemical properties as described below:

1. Anticancer effect

Andrographolide, the major bioactive compound of Kalmegh showed prominent effects on malignant cells due to hindrances in the proliferation of cells, arrest of the cell cycle, or cell

discrepancy. Through induction of programmed cell death of malignant cells, these compounds also enhance the immune system. The anticancer ability of AD in colon cancer cells (HT-29) was evaluated by Khan *et al.* (2018) and a reduction in cell viability was observed. In a time and dose dependant manner, they observed reduced viability of the cells. The cell cycle in the G2 and M phases was surprisingly interrupted by AD at lower doses. While the cell cycle at the G0/G1 phase was arrested at a higher amount. Through ameliorating intracellular free radical levels and disruption of mitochondrial membrane potential, these phytoconstituents caused apoptosis of the cancer cells. AD along with another flavonoid isolated from Kalmegh leaves remarkably reticent U251 (CNS) and M14 (melanoma) human carcinoma cells and thereby proven the anticancer effect of the herb (Agarwal, 2015).

Diterpenoids along with andrographolide and isoandrographolide isolated from Kalmegh have also been explored by Chen and Colleagues (2009) taking human leukaemia (HL-60) cells. These two compounds were more effective compared to others. A different flavonoid, 7, 8-dimethoxy-2'-hydroxy-5-O-β-d-glucopyranosyloxyflavone, with a dose value (IC₅₀) of 3.50 μM extracted from the aerial portions of the herb, revealed persuasive antiproliferative activity against leukaemia cells. An improvement in G0/G1 phase cells and a significant decline in the cell amount at the Synthesis Phase and G2 and M stages were observed against HL-60 cells with the use of andrographolide at a dose of 12 μg/mL.

The effective cytotoxic activity of the herbal extracts has been studied by Geethangili *et al.* (2008) against several human cancer cells such as lymphocytic (Jurkat), prostate (PC-3), hepatoma (HepG2), and colon cancer cells. Noticeably inhibition in the proliferation of HT-29 colon cancer cells was observed with the dichloromethane fraction of the extract. Inhibition of human colorectal carcinoma (CRC) Lovo cell growth by andrographolide was also reported by Shi *et al.* (2011). Induction in the expression of inhibitory proteins (p16, p21, and p53) of the cell cycle and arrest of the G1-S phases is considered to be responsible for this. The activity of cyclin D1 along with Cdk4 and cyclin A1/Cdk2 necessary for the

transition from the G1 to S phase has been overwhelmed by these proteins. Growth suppression, CRC cell invasion, and stimulation of apoptosis have been shown by andrographolide recently.

AD repressed the proliferation of lung cancer cells through a reduction in the level as well as a transformation of the growth factor (Luo *et al.*, 2014). Inhibition of melanoma tumour enlargement and metastasis through apoptosis and arrest of the melanoma cell cycle at the G-1 phase has also been shown by AD. In other ways, inhibition of TLR4/NF- κ B signaling pathways, followed by inhibition of mRNA and Bcl-6 and CXCR4 protein expression, is thought to be the underlying mechanism for this activity (Zhang *et al.*, 2014).

2. Antihyperglycemic effect

Effective antihyperglycemic action has been shown by AP extracts and andrographolide with a reduction of blood glucose levels through α -glucosidase and α -amylase inhibition. Besides monitoring blood glucose levels, the compounds in a dose-dependent manner can also effectually prevent the onset of insulinitis. Consequently, in NOD mice, diabetes development was suppressed and delayed. By improving glucose exploitation and oxidation, AP has been found to lower blood glucose levels in type 2 diabetic rats. Liver restoration of insulin signaling molecules and lower serum lipid levels are also responsible for this activity (Augustine *et al.*, 2014). Additionally, andrographolide controls the T Helper cells balance, which enables it to restrict T-cell insinuation into pancreatic cells and maybe avert β -cell death. Thereby, preventing the expansion of type 1 diabetes. For the antihyperglycemic action, stimulation of the sugar uptake and peripheral tissues oxidation with an increase in insulin level is also taken into consideration.

In both insulin-deficient diabetics and healthy rats, AP had a diminishing effect on blood sugar levels. In diabetic rats, andrographolide significantly enhanced β -cell functioning, GLUT4 translocation, and blood glucose levels. There was an ominous decrease in the fasting blood glucose in humans upon administration of Kalmegh extracts. Another bioactive constituent, 14-deoxy-11, 12-didehydroandrographolide, has also

demonstrated antihyperglycemic action. Therefore, researchers' main focus will be on finding more antihyperglycemic chemicals in Kalmegh along with other medicinal plants to develop a better diabetic treatment alternative.

3. Anti-hyperlipidemic effect

The major cause of atherosclerosis, which results in heart attack and stroke, is hyperlipidemia. Several medicinal plants have been utilized, either alone or in combination, for the treatment of *Diabetes mellitus* (DM) since time immemorial. However, in order to confirm the safety and efficacy of these medicinal plants further scientific and clinical studies are needed (Fallah *et al.*, 2023). Chen *et al.* (2020) found that andrographolide and neo andrographolide from AD have antihyperlipidemic properties. Reports by Yang and Song (2014), mentioned the fruitful efficacy of andrographolide and neo andrographolide on hyperlipidemic mouse models. In a dose-dependent way, these two substances diminished the cholesterol level, which can be confirmed with a decrease in the enzymes aspartate transaminase and alanine transaminase. Due to the various regulation of iNOS as well as eNOS expression in the aorta of hyperlipidemic rats, lipid and lipoprotein-reducing actions of the substances are liable to increase. It is necessary to concentrate future research on the concurrent signaling pathway and molecular mechanism.

4. Cardiovascular effect

According to Wong *et al.* (2020), *A. paniculata* and andrographolide have bioactivities that decrease the inflammatory response, oxidative stress, apoptosis, cardiac fibrosis, and endothelial dysfunction. By inhibiting the inductive phase of the inflammatory response, mediated by several signaling molecules such as NF- κ B, PI3K/ Akt, MAPK, and STAT3, the phytoconstituents reduce the signs of myocardial damage. A possible mechanism for the specific action might be the effect on oxidative stress caused by activating the nuclear transcription factor, Nrf-2, and decreasing the enzymes that produce free radicals. Additionally, the phytoconstituents have blocked profibrotic growth factors, which has reduced heart fibrosis and enhanced endothelial and fibrinolytic function (Wong *et al.*, 2020).

5. Antimalarial and filaricidal activity

Antimalarial action of Kalmegh root xanthenes against *Plasmodium falciparum* and *Plasmodium berghei* on animal models (Swiss Albino mice) have been investigated by Dua *et al.* (2004). After treating the mice with a dose level of 30 mg/kg, a generous reduction (62%) in parasitaemia was observed. 1, 2-dihydroxy-6, 8-dimethoxyxanthone, with a dose level of IC₅₀ > 32 µg/mL was noncytotoxic against mammalian cells in an *in-vitro* cytotoxicity assay. Filariasis, a condition in which there is an obstruction of the lymph channels that will lead to Elephantiasis can be efficiently inhibited with the herbal extracts. Four of the potent xanthenes such as 4, 8-dihydroxy-2, 7-dimethoxy xanthone, 1, 8-dihydroxy-3, 7-dimethoxy xanthone, 3, 7, 8- trimethoxy-1-hydroxyxanthone, and 1, 2- dihydroxy-6, 8-dimethoxyxanthone were reported in the roots of the herb. However, substantial antiplasmodial activity against adult worms of *Brugia malayi* was reported by 1, 2-dihydroxy-6, and 8-dimethoxy-xanthone. Though, clues for the pharmacological targets along with the mechanism of action of this compound on *P. falciparum* are still unclear. However, the regulation of a transcription factor is considered to be responsible for this phenomenon. Erythrocytes, upon infected with *P. falciparum*, there was an induction of NF-κB regulated inflammatory pathways in human cerebral endothelium has been observed. For effective regulation of malaria, there is a need for the re-evaluation of probable anti-malarial activity of andrographolide against the blood stage of the plasmodial life cycle.

6. Antidiarrheal effects

Diarrhea is the second leading cause of death, especially among children under five years old in developing countries. *S. flexneri*, *S. aureus*, *E. coli*, *S. typhi*, and *C. albicans* are the foremost causative agents of diarrhea in humans (Ashrafuzzaman *et al.*, 2016). Several plant extract comprises pharmacologically active substances with antidiarrheal properties. AP extracts exhibited substantial effects against *E. coli* bacterial infections. A substantial effect against *E. coli* bacterial infections has been reported. In a case study, patients with acute bacterial diarrhoea were given a 500 mg dose of andrographolide for six

days on a daily basis. It was found that the patients responded favourably to the treatment with an overall effectiveness of 91.3%. Due to its antibacterial activity, the herbal extract was effective in bacterial dysentery as well as diarrhea (Perumal Samy *et al.*, 2007).

7. Antibacterial activity

Deaths due to microbial infections were investigated and reported around 9.2 million in 2013, accounting for 17% of overall mortality (Gupta *et al.*, 2019; WHO, 2013). The microbes acquire resistance to numerous antimicrobial drugs and this is considered to be the sole cause for the ineffectiveness of the drugs. To fight the health problems related to bacterial infections, there should be an imperious need for research on other therapeutic agents as an alternative source to existing ones (Brown, 2015; Ncube *et al.*, 2007). Due to their immense therapeutic activities, plant based antibacterial components are thus a suitable remedy for infectious diseases (Shakeri *et al.*, 2018).

The isolated phytoconstituents andrographolide from AP showed significant antimicrobial activity. Various organic solvent extracts of AP flowers exhibited antimicrobial action toward *S. agalactiae*, *S. aureus*, and *E. coli* were reported by Sivananthan (2013). An inhibitory effect and thus antimicrobial activity of Kalmegh extract against the urinary tract pathogens for example *E. coli*, *P. aeruginosa*, *K. pneumonia*, and *S. aureus* has been reported by Murugesan *et al.* (2018). However, maximum inhibitory action was reported against *E. coli*.

Discussion

There is mention of *Andrographis paniculata* (AP) possessing potent phytoconstituents in altered traditional systems of medicines. Due to various pharmacological activities, the herb has been used as a remedy for hepatic issues, malaria, common colds, cardiovascular diseases, leprosy, stomach problems, etc. The plant has been used to treat hepatic issues, malaria, common colds, cardiovascular diseases, leprosy, stomach problems, etc. due to various pharmacological activities. The prime component accountable for most of the pharmacological actions of the drug is Andrographolide- a diterpene lactone.

Along with other diterpenoids isolated from AP, andrographolide, and isoandrographolide have been reported for their antiproliferative activities by many authors against mammalian cell lines. Potent antiproliferative activity by parts of AP against leukaemia cell lines has been reported. An improvement in cells (G0/G1 phase) and a considerable decline in cell amount against HL-60 cells were mentioned with the use of andrographolide. The dichloromethane fraction of the extract reported a considerable inhibition in the proliferation of HT-29 colon cancer cells. A direct inhibitory effect on cancer cells was employed by andrographolide and its analogues due to induction in the expression of cell cycle inhibitory proteins along with depressing cyclin-dependent kinase (Cdk). As a result, the progression of the cell cycle has been blocked at various stages. In multiple myeloma cells, an inhibition in cell proliferation, and apoptosis, as well as an enhancement in the caspase cascade activation was perceived. AD at a dose of 5µg/g showed *in vivo* anticancer activity in B16 melanoma mouse cells through inhibition of the TLR4/NF-κB signaling pathway. Reports regarding *in vitro* anticancer activity by AD have also been available in human myeloma cell (OPM1).

AP decreases the blood sugar level by escalating its utilization and oxidation. Apart from this insulin signaling molecules restoration in the liver and fall in the serum lipid levels indicate the positive effects of the compound (Augustine *et al.*, 2014). The blood sugar level lowering ability due to inhibition of α-glycosidase and α-amylase is another way that proves the antihyperglycemic effects of the AP extracts and andrographolide. Whereas, Yu *et al.*, 2003; reported that the increase of plasma glucose in rats has significantly been attenuated by Andrographolide. Andrographolide and neoandrographolide- two of the potent phytoconstituents have shown hyperlipidemic activity in animal models (mice) (Yang *et al.*, 2014). There was a significant reduction of aspartate and alanine transaminase levels in the plasma compared with simvastatin. The lipid and lipoprotein-reducing effects of the compounds in hyperlipidemic rats are possible due to various regulation steps of iNOS and eNOS expression. The active constituents along with the aqueous extracts

of AP exhibited platelet anti-aggregation activity against *in vitro* mouse models (Thisoda *et al.*, 2006). AP has the potential to enhance NO, cyclic GMP, and SOD activity (Wang *et al.*, 2020).

Andrographolide showed a potential beneficial effect against H9C2 cardiomyocytes. Reports were there on the effective doses for *Kalmegh* herbal extract with treatment duration of 7-31 days against myocardial injury. Thus, *Kalmegh* can be considered as an alternative source for the treatment of cardiovascular diseases. However, the effectiveness of these phytoconstituents from the herb against myocardial injury in humans along with clinical trials is yet to be investigated. The mice upon treatment with the herbal extract of andrographis showed a substantial reduction in parasitaemia. The ring stage of the parasite, during the erythrocytic life cycle, is considered to be the key point where the activity of andrographolide was found to be prominent. Protein and nucleic acid synthesis are the key points in the parasite life cycle, upon which the mechanism of action of this compound relies. The efficacy of AP solvent extracts as an antibacterial agent in urinary tract pathogens have been reported by Murugesan *et al.* (2018). The herb showed an overall effectiveness of 91.3% among patients with acute bacterial diarrhoea after treatment for six days.

Researchers, around the globe attain various leads by structurally modifying andrographolide due to the variety of biological activities shown by the herb. The pharmacological activities of numerous andrographolide derivatives have been evaluated that have emerged in recent times. A pilot-scale clinical studies has confirmed the safety of the herb. The herb's efficacy against other diseases needs to be evaluated further in all age group populations. However, studies that have comprehensively summarized or analyzed *A. paniculata* and its derivatives have been minimal. As a prerequisite, there is a need for deep research to assess the potential of the plant in clinical practices. In conclusion, this review highlights the chief eminence of *Kalmegh* as an established medicinal herb. The various pharmacological activities of the herb make it valuable in ameliorating altered diseases and lay out crucial directions for future research.

REFERENCES :

- Agarwal, D. 2015. A new anticancer flavonoid from leaves of *Andrographis paniculata*. *J. Glob. Biosci.*, **4**(5): 2355-2360.
- Ashrafuzzaman, M.D., Raju, G.S., Abeer, M.I.U., Seeam, S.M., Salahuddin, A.Z.M., and Debnath, D., Snigdha, H.M.S.H., Sawan, B.U., Rana, S. M.M. 2016. Antidiarrheal Activity of Three Medicinal Plants in Swiss Albino Mice. *International Journal of Biomedicine*, **6**(3):233-236. [https://doi.org/10.21103/article6\(3\)_oa16](https://doi.org/10.21103/article6(3)_oa16).
- Augustine, A.W., Narasimhan, A., Vishwanathan, M. and Karundevi, B. 2014. Evaluation of antidiabetic property of *Andrographis paniculata* powder in high fat and sucrose-induced type-2 diabetic adult male rat, *Asian Pacific Journal of Tropical Disease*, **4**(1):140-147. [https://doi.org/10.1016/S2222-1808\(14\)60429-1](https://doi.org/10.1016/S2222-1808(14)60429-1).
- Brown, D. 2015. Antibiotic resistance breakers: can repurposed drugs fill the antibiotic discovery void? *Nat. Rev. Drug Discov.*, **14**(12):821-832. <https://doi.org/10.1038/nrd4675>. PMID: 26493767.
- Calabrese, C., Berman, S.H., Babish, J.G., Ma, X., Shinto, L., Dorr, M., Wells, K., Wenner, C.A. and Standish, L.J. 2000. A phase I trial of andrographolide in HIV positive patients and normal volunteers, *Phytother. Res.*, **14**(5): 333-338. doi: 10.1002/1099-1573 (200008)14:5<333::aid-ptr584>3.0.co;2-d. PMID: 10925397.
- Chen, C. C., Lii, C.K., Lin, Y.H., Shie, P.H., Yang, Y.C., Huang, C.S. and Chen, H.W. 2020. *Andrographis paniculata* improves insulin resistance in high-fat diet-induced obese mice and TNF α -treated 3T3-L1 adipocytes. *Am. J. Chin. Med.* **48**(5): 1073-1090. doi: 10.1142/S0192415X20500524. PMID: 32668968.
- Chen, J.X., Xue, H.J. and Ye W.C., Fang, BH, Liu, YH, Yuan, SH, Yu P. and Wang, YQ. 2009. Activity of andrographolide and its derivatives against influenza virus in vivo and in vitro, *Biol Pharm Bull.*, **32**(8): 1385-1391. doi: 10.1248/bpb.32.1385. PMID: 19652378.
- Chopra, R.N., Nayar, S.L. and Chopra, I.C. 1956. Glossary of Indian Medicinal Plants. Council of Scientific and Industrial Research, New Delhi.
- Dua, V.K., Ojha, V.P., Roy, R., Joshi, B.C., Valecha, N., Usha Devi, C., Bhatnagar, M.C., Sharma, V.P. and Subbarao, S.K. 2004. Anti-malarial activity of some xanthenes isolated from the roots of *Andrographis paniculata*, *Journal of Ethnopharmacology*, **95**(2-3): 247-251. <https://doi.org/10.1016/j.jep.2004.07.008>. PMID: 15507344.
- Fallah, H.H., Mohamadzadeh, K., Kianbakht, S., Mohammadi, S.M., Ahvazi, M., Hooseini, M. S., Khalili, N., Foroutan, B., Saberi, M., Baghaei, A., Mohtashami, R. 2023. Antihyperglycemic efficacy and safety of AKROPOL, a Persian medicine poly-herbal extract mixture, in the treatment of type 2 diabetic patients: a randomized, double-blind and placebo-controlled clinical trial. *J. Med. Plants*, **22** (86):1-13
URL: <http://jmp.ir/article-1-3438-en.html>
- Gabrielian, E.S., Shukarian, A.K., Goukasova, G.I., Chandanian, G.L., Panossian, A.G., Wikman, G., and Wagner, H. A. 2002. A double-blind, placebo-controlled study of *Andrographis paniculata* fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. *Phytomed*, **9**(7):589-597. <https://doi.org/10.1078/094471102321616391>. PMID: 12487322.
- Geethangili, M., Rao, Y.K., Fang, S.H., and Tzeng, Y.M. 2008. Cytotoxic constituents from *Andrographis paniculata* induce cell cycle arrest in Jurkat cells. *Phytother Res*, **22**(10):1336-1341. <https://doi.org/10.1002/ptr.2493>. PMID: 18546141.
- Gowthami, R., Sharma, N., Pandey, R. and Agrawal, A. 2021. Status and consolidated list of threatened medicinal plants of India. *Genet. Resour. Crop Evol.*, **68**: 2235-2263.
- Gupta, M., Sharma, R. and Kumar, A. 2019. Comparative potential of Simvastatin, Rosuvastatin, and Fluvastatin against bacterial infection: an in silico and in vitro study. *Orient. Pharm. Exp. Med.*, **19**:259-275. <https://doi.org/10.1007/s13596-019-00359-z>.
- Hancke, J., Burgos, R., Caceres, D. and Wilkman, G. 1995. A double-blind study with a new

- mono drug Kan Jang: Decrease of symptoms and improvement in the recovery from common colds. *Phytother. Res.*, **9**:559-562. <https://doi.org/10.1002/ptr.2650090804>
- Iruretagoyena, M.I., Tobar, J.A., Gonzalez, P.A., Sepúlveda, S.E., Figueroa, C.A., Burgos, R.A., Hancke, J.L. and Kalergis, A.M. 2005. Andrographolide interferes with T cell activation and reduces experimental autoimmune encephalomyelitis in the mouse, *J. Pharmacol Exp Ther.*, **312**(1):366-372. <https://doi.org/10.1124/jpet.104.072512>. PMID: 15331658.
- Kanjilal, P.B., Bordoloi, S., Kalita, R., Burman, P. and Singh, R.S. 2002. Cultivation practices of *kalmegh* (*Andrographis paniculata*) and spiderling (*Boerhaavia diffusa*) in Assam, India. *Recent progress in medicinal plants*. **5**:175-180.
- Khan, I., Khan, F., Farooqui, A. and Ansari, I.A. 2018. Andrographolide exhibits anticancer potential against human colon cancer cells by inducing cell cycle arrest and programmed cell death via augmentation of intracellular reactive oxygen species level. *Nutr. Cancer.*, **70**(5): 787-803. <https://doi.org/10.1080/01635581.2018.1470649>. PMID: 29781715.
- Koteswara Rao, Y., Vimalamma, G., Venkata Rao, C., and Tzeng, Y.M. 2004. Flavonoids and andrographolides from *Andrographis paniculata*. *Phytochemistry*, **65**:2317-2321. <https://doi.org/10.1016/j.phytochem.2004.05.008>
- Kumar, A., Amit, A., Sujatha, M., Murali, B. and Anand, M.S. 2002. Effect of aging on andrographolide content in Kalmegh. *Journal of Natural Remedies*. **2**(2):179-181. <https://doi.org/10.18311/jnr/2002/145>
- Kumar, R.N., Chakraborty, S. and Nirmal, J.I. 2011. Methods to break seed dormancy of *Andrographis paniculata* (Burm. f. Nees): an important medicinal herb of tropical Asia, *Asian Journal of Experimental Biological Sciences*, **2**(1):143-146.
- Li, W., Xu, X., and Zhang, H., Ma, C., Fong, H., van Breemen, R. and Fitzloff, J. 2007. Secondary metabolites from *Andrographis paniculata*, *Chemical and Pharmaceutical Bulletin*, **55**(3):455-458.
- Luo, X., Luo, W., Lin, C., Zhang, L. and Li, Y. 2014. Andrographolide inhibits proliferation of human Lung cancer cells and the related mechanisms. *Int. J. Clin. Exp. Med.*, **7**(11):4220-4225. PMID: 25550934; PMCID: PMC4276192.
- Mall, T.P. and Tripathi, S.C. 2016. Kalpnath-A trusted potent ethnomedicinal plant from North central Tarai forests of U.P. India. *World Journal of Pharmaceutical Research*, **5**(1): 734-741.
- Martin, K.P. 2004. Plant regeneration protocol of medicinally important *Andrographis paniculata* (Burm. f.) Wallich ex Nees via somatic embryogenesis, *In Vitro Cell. Dev. Biol.-Plant*, **40**(2):204-209. <https://doi.org/10.1079/IVP2003520>
- Meena, B.R., Meena, D., Kapoor, A. and Kumar, A. 2017. Dynamics of growth parameter and yield of *kalmegh* (*Andrographis paniculata*) under different weed control techniques. *Int J Chem Stud.*, **5**(6):773-776.
- Mishra, K., Dash, A.P., Swain, B.K. and Dey, N. 2009. Antimalarial activities of *Andrographis paniculata* and *Hedyotis corymbosa* extracts and their combination with curcumin, *Malar J.*, **8**(1):26. <https://doi.org/10.1186/1475-2875-8-26>. PMID: 19216765; PMCID: PMC2650700.
- Mishra, S., Sangwan, N. and Sangwan, R. 2007. *Andrographis paniculata* (Kalmegh): a review, *Pharmacog Rev.*, **1**(2):283-298.
- Murugesan, R., Sigamani, A., Sengodan, K. and Raja, V. 2018. *In vitro* antibacterial activity of ethanol extract of *Andrographis paniculata* against uropathogens. *World J. Pharm. Pharm. Sci.*, **7**:922-929.
- Ncube, N.S., Afolayan, A.J. and Okoh, A.I. 2007. Assessment techniques of antimicrobial properties of natural compounds of plant origin: current methods and future trends. *Afr. J. Biotechnol.*, **7**(12):1797-1806. <https://doi.org/10.5897/AJB07.613>
- Nemade, S., Mohod, N.B, Wankhade, S.G. and Paturde, J.T. 2003. Effect of planting and harvesting dates on yield and quality of *kalmegh* (*Andrographis paniculata*), *Journal of Medicinal and Aromatic Plant Sciences*, **25**(4):981-983.

- Niranjan, A., Tewari, S.K. and Lehri, A. 2010. Biological activities of Kalmegh (*Andrographis paniculata* Nees) and its active principles-Areview, *Indian Journal of Natural Products and Resources*, **1**(2):125-135.
- Pandey, J., Saini, V.K. and Raja, W. 2019. Evaluation of phytochemical analysis of *Andrographis paniculata* leaf and stem extract, *wjpls*, **5**(2):188-190.
- Perumal Samy, R., Thwin, M.M. and Gopalakrishnakone, P. 2007. Phytochemistry, Pharmacology and Clinical Use of *Andrographis paniculata*. *Natural Product Communications*, **2**(5): 607-618.
- Ram, D., Chandra, R. and Kumar, B. 2008. Effect of spacing and organics on growth and herbage yield of kalmegh (*Andrographis paniculata* Wall. Ex. Nees). *Prog. Hort.*, **40**(1):69-73.
- Rani, B.J. and Sridhar, V. 2005. Record of arthropod pests of Kalmegh, *Andrographis paniculata* a medicinal plant. *Insect Env.*, **11**(2):89-91.
- Samy, R.P., Thwin, M.M., Gopalakrishnakone, P. and Ignacimuthu, S. 2008. Ethnobotanical survey of folk plants for the treatment of snakebites in Southern part of Tamilnadu, *India. J. Ethnopharmacol*, **115**(2): 302-312. <https://doi.org/10.1016/j.jep.2007.10.006>. PMID: 18055146.
- Semwal, M.P., Pandey, S.T., Singh, V.P., Kumar, A., Gautam, P., Chaudhary, S. and Singh, D. 2016. Influence of planting geometries and weed control practices on growth and herbage yield of Kalmegh (*Andrographis paniculata* Nees.). *Journal of Medicinal Plants Studies*, **4**(6):162-166.
- Shakeri, A., Sharifi, M.J., Bazzaz, F.B.S., Emami, A., Soheili, V., Sahebkar, A. and Javad, A. 2018. Bioautography detection of antimicrobial compounds from the essential oil of *salvia Pachystachys*. *Curr. Bioact. Compd.*, **14**(1):80-85. <http://dx.doi.org/10.2174/1573407212666161014132503>
- Sharma, A., Krishan, L. and Handa, S.S. 1992. Standardization of the Indian crude drug Kalmegh by high-pressure liquid chromatographic determination of andrographolide. *Phytochemical Analysis*, **3**:129-31. <https://doi.org/10.1002/pca.2800030308>
- Sharma, S.N., Sahu, S., Jha, Z. and Sharma, D.K. 2012. Evaluation of seasonal variation in relation to secondary metabolite and biomass production of *Andrographis paniculata*. *J. Nat. Remedies*, **12**:39-46. <https://doi.org/10.18311/jnr/2012/35>.
- Shi, G., Zhang, Z., Zhang, R., Zhang, X., Lu, X., Yang, J., Zhang, D., Zhang, Z., L., X. and Ning, G. 2011. Protective effect of andrographolide against Concaravatin A-induced liver injury. *Naunyn Schmiedebergs Arch. Pharmacol.*, **385**: 69-79.
- Singha, P.K., Roy, S. and Dey, S. 2003. Antimicrobial activity of *Andrographis paniculata*. *Fitoterapia*, **74**:692-694. [https://doi.org/10.1016/s0367-326x\(03\)00159-x](https://doi.org/10.1016/s0367-326x(03)00159-x). PMID: 14630176.
- Siripong, P., Kongkathip, B., Preechanukool, K., Picha, P., Tunsuwan, K. and Taylor, W.C. 1992. Cytotoxic diterpenoid constituents from *Andrographis paniculata*, Nees leaves. *Journal of the Scientific Society of Thailand*, **18**:187-194.
- Sivananthan, M. 2013. Antibacterial and antifungal activity of flowers of *Andrographis paniculata*. *Int. J. Pharm. Tech. Res.*, **5**(3):1399-1403.
- Suganthy, M. and Sakthivel, P. 2013. Field evaluation of botanicals on pest complex of *Solanum nigrum* Linn. *Madras Agri J.*, **100**(4-6):592-596.
- Thisoda, P., Rangkadilok, N., Pholphana, N., Worasuttayangkurn, L., Ruchirawat, S. and Satayavivad, J. 2006. "Inhibitory effect of *Andrographis paniculata* extract and its active diterpenoids on platelet aggregation," *European Journal of Pharmacology*, **553**(1-3):39-45. <https://doi.org/10.1016/j.ejphar.2006.09.052>. PMID: 17081514.
- Tipakorn, N. 2002. Effects of *Andrographis paniculata* (Burm. f.) Nees on performance, mortality, and coccidiosis in broiler chickens. Ph. D. thesis. Institute of Animal Physiology and Animal Nutrition, Georg-August-Universitat, Gottingen, 2002.
- Varier, P.S. 1993. *Indian Medicinal Plants* Vol. I. Warriar PK, Warriar PK, Nambiar VPK, Ramankutty C. (Eds.) Arya Vaidya Sala,

- Kottakkal. Orient Longman, Madras, p. 135-138.
- Verma, H., Negi, M.S., Mahapatra, B.S., Shukla, A. and Paul, J. 2019. Evaluation of an emerging medicinal crop *Kalmegh* [*Andrographis paniculata*(Burm. F.) Wall. Ex. Nees] for commercial cultivation and pharmaceutical & industrial uses: A review. *Journal of Pharmacognosy and Phytochemistry*, **8**(4): 835-848.
- Vijaylaxmi, S. Dandin. and Murthy, H.N. 2012. Regeneration of *Andrographis paniculata* Nees: analysis of genetic fidelity and andrographolide content in micro propagated plants, *African Journal of Biotechnology*, **11**(61):12464-12471. <http://dx.doi.org/10.5897/ajb12.1551>
- Wang, S., Li, H., Chen, S., Wang, Z., Yao, Y., Chen, T., Ye, Z. and Lin, P. 2020. Andrographolide induces apoptosis in human osteosarcoma cells via the ROS/JNK pathway. *Int. J. Oncol.*, **56**(6): 1417-1428. <https://doi.org/10.3892/ijo.2020.5032>. PMID: 32236589; PMCID: PMC7170044.
- Wankhade, S.G., Khode, P.P, Wanjari, S.S., Paturde, J.T. and Sakure, S.M. 2005. Herbage yield and quality of *kalmegh* (*Andrographis paniculata*) as influenced by Time of planting and Harvesting. *Indian J Agric. Res.*, **39** (4):303-306.
- Weiming, C. and Xiaotian, L. 1982. Deoxyandrographolide 19 β -D-glucoside from the leaves of *A. paniculata*, *Planta Medica*, **45**(4):245-246. <https://doi.org/10.1055/s-2007-971383>. PMID: 17396922.
- Wen, W.C., Yueh, K.H. and Fong, L.B. 2010. Anti-inflammatory activity of new compounds from *Andrographis paniculata* by NF- κ B transactivation inhibition. *J. Agric Food Chem*, **58**(4): 2505-2512. <https://doi.org/10.1021/jf903629j>
- WHO, 2013. Methods and Data Sources for Global Burden of Disease Estimates 2000-2011. Department of Health Statistics and Information Systems, Geneva.
- Wuart, C., Kumar, K., Yusof, M.Y., Hamimah, H., Fauzi, Z.M. and Sulaiman, M. 2005. Antiviral properties of ent-labdene diterpenes of *Andrographis paniculata* Nees, inhibitors of herpes simplex virus type 1. *Phytotherapy Research*, **19**(12):1069-1070. <https://doi.org/10.1002/ptr.1765>. PMID: 16372376.
- Wong, J.H., Ng, T.B., Chan, H.H.L., Liu, Q., Man, G.C.W. and Zhang, C.Z. 2020. Mushroom Extracts and Compounds with Suppressive Action on Breast Cancer: Evidence from Studies Using Cultured Cancer Cells, Tumor-Bearing Animals, and Clinical Trials. *Appl. Microbiol. Biotechnol*, **104** (11):4675-703. doi: 10.1007/s00253-020-10476-4.
- Yang, E.J. and Song, K.S. 2014. Andrographolide, a major component of *Andrographis paniculata* leaves, has the neuroprotective effects on glutamate-induced HT22 cell death. *J. Funct. Foods*, **9**:162-172.
- Yu, B.C., Hung, C.R., Chen, W.C. and Cheng, J.T. 2003. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. *Planta Med.*, **69**(12):1075-9. doi: 10.1055/s-2003-45185. PMID: 14750020.
- Zhang, C.Y. and Tan, B.K. 1997. Mechanisms of cardiovascular activity of *Andrographis paniculata* in the anaesthetized rat. *Journal of Ethnopharmacology*, **56**(2):97-101. [https://doi.org/10.1016/s0378-8741\(97\)01509-2](https://doi.org/10.1016/s0378-8741(97)01509-2). PMID: 9174969.
- Zhang, Q.Q., Zhou, D. L., Ding, Y., Liu, H.Y., Fang, H.Y., Gu, Q.L., He, X.D., Qi, C.L., Lan, T., Li, J.C., Gong, P., Wu, X.Y., Lei, Y., Yang, X., Li, W.D. and Wang, L.J. 2014. Andrographolide inhibits melanoma tumor growth by inactivating the TLR4/NF- κ B signaling pathway, *Melanoma Res.*, **24**: 545-555. <https://doi.org/10.1097/cmr.000000000000117>. PMID: 25244079
- Zhao, H.Y. and Fang, W.Y. 1991. Antithrombotic effects of *Andrographis paniculata* Nees in preventing myocardial infarction. *Chinese Medical Journal (English)*, **104**(9):770-775. PMID: 1935360.