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Review Article

Ethnopharmacological review of kalmegh for anticancer activity

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ABSTRACT

The cultivation of Kalmegh (*Andrographis paniculata*), a plant with numerous therapeutic benefits, has increased its significance as a medicinal plant. Given the plant's beneficial properties, it can be strongly recommended as a secure, crucial medicinal herb for people. There are many different chemical components in this herb, but the primary ones are lactones, diterpenoids, diterpene glycosides, flavonoids, and flavonoid glycosides. It possesses a wide range of pharmacological effects, including antibacterial, hepatoprotective, antitumor, anticancer, hypoglycemic, immunomodulatory, and hypotensive actions. This study describes the past and status of research on Andrographis paniculate palnt's therapeutic utilisation. It also emphasizes at compiling vast pharmacological applications to make the potential image of *Andrographis paniculata* as a multipurpose medicinal agent. This ethnopharmacological review deals with anticancer activity of Kalmegh or *A.paniculata.*

1. Introduction

Most of the world's population, particularly in underdeveloped nations, mainly relies on traditional doctors and medicinal plants to meet their basic healthcare needs.[1] The connection to conventional medications causes several issues. Because of this, experts have recently revised their assessments of numerous species of medicinal plants based on differences in their species and therapeutic potential. Therefore, it is essential to review the earlier literature that has been published on species in order to refresh our knowledge of them. The *Andrographis paniculata* is one of them (Acanthaceae). It is made up of roughly 40 species and has been around since the millennium years.

It is inherent to India Srilanka and also distributed in different regions of Southeast Asia, China, America, and the West Indies. It grows well in almost all types of soil thus it is widely distributed. It has been cultivated due to its renowned therapeutic potential.[2] The aerial parts and roots of *A.paniculata* have been widely used in treating various maladies. It is known to be Mahatikta in (Sanskrit), Kiryato in (Gujarati), Mahatita in (Hindi) and Kalmegh in (Bengali).[3] Various studies have been conducted by the researchers followed by the reports about therapeutic potential possessed by this herb. The phytochemical studies revealed that *A.paniculata* contains various compounds like diterpenoid lactones, flavonoids and miscellaneous compounds. Due to their presence, it possesses a wide range of pharmacological properties.[4,5] This review presents the therapeutic potential, phytochemistry and pharmacological properties of *A.paniculata* (extracts and compounds) including antimicrobial, antiprotozoal-ininflammatory storyantioxidant, antidiabetic, antiinfective, immunostimulant, hepatorenal protective, sex hormone modulatory, liver enzymes modulatory, cytotoxic,

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insecticidal, neuroprotective, anticancer, antipyretic and anti-platelet activities. Furthermore, this review confers some toxicological aspects of *A. paniculata.*

1.1. Taxanomic Classification

Fig. 1:

1. Kingdom: Plantae, Plants;
2. Subkingdom: Tracheobionta, Vascular plants;
3. Super division: Spermatophyta, Seed plants;
4. Division: Angiosperma
5. Class: Dicotyledonae
6. Subclass: Gamopetalae
7. Series: Bicarpellatae
8. Order: Personales
9. Tribe: Justicieae
10. Family: Acanthaceae
11. Genus: Andrographis
12. Species: paniculata

Kalmegh is a little, erect, annual, terrestrial herb that grows to a height of 1-3 feet. The stem is woolly hairy in the top juvenile parts, dark green, heavily branched, sharply quadrangular, smooth from the lower part with longitudinal furrows, and. Smooth, opposite, linear to lanceolate, short petioled, with narrowing ends, 1.5–2.5 inches long, and 0.5-0.75 inches wide are the characteristics of the leaves. Small, petiolate, white, light purplish, or with purple spots are the flowers. Spreading (terminal and axillary) panicled recemes that are 2-4 inches long make up the inflorescence. Five-linear, lanceolate, and woolly-haired describe the calyx. The corolla tube is small and about 6 mm long; the limb is bi-labiate and longer than the tube. Two far-extended stamens with two embedded in the neck; one anther is essentially bearded. Fruits are the erect capsules of linear-oblong some, 1 - 2 cms long and, 2-5 mm wide and acute at both ends. The unriwooly-haired wool haired whereas the ripe one is smooth. Seeds are small, numerous, sub-quadrate and yellowish brown in color. The plants bear flowers and fruits during the months of April-May (Grishma Ritu) and September-October (Sharad Ritu).

1.2. Therapeutic uses of andrographis paniculata

The components of *Andrographis paniculata* have been used as a traditional medicine in Asia for millennia to cure a wide range of conditions, including stomachaches, inflammation, pyrexia, and intermittent fevers. The entire plant of *A.paniculata* has been used as a remedy for toxic bug stings and snakebites. In addition, dyspepsia, influenza, dysentery, malaria, and respiratory infections are all treated with it[6–9] Traditional treatments for infections like fever, colic discomfort, appetite loss, irregular stools, and diarrhoea have included.[10] The common cold, high blood pressure, diabetes, cancer, and malaria were all treated with aerial component decoctions.[11] The therapeutic use of several *A.paniculata* components are listed in Table 1.

Table 1: Therapeutic uses of different parts of *Andrographis paniculata*

S. No	Part	Therapeutic Uses
1.	Whole Plant	Poisonous sting treatment, dyspepsia, malaria, and respiratory infections
2.	Aerial Part	Diabetes, hypertension, cancer, and urinary tract infections
3.	Leaf	Fever, colic pain, mouth ulcers, hepatitis, tuberculosis, and diarrhea
4.	Root	Febrifuge, tonic, and anthelmintic

It has been employed as a herb with anti-cold properties to reduce body heat and fever. Additionally, it aids in the removal of pollutants from the body.[12] The tribal people of Tamilnadu in India used this herb to treat a wide range of illnesses, including dysmenorrhoea, leucorrhea, pre- and post-natal care, malaria, jaundice, gonorrhoea, wounds, cuts, boils, and skin conditions[13–15]Table 2 lists the various ways these tribal members use *A.paniculata.*

1.3. Phytochemistry

It has been used as a cold-fighting herb to lower body heat and fever. Additionally, it helps the body rid itself of contaminants[16] This herb was utilised by the tribal people of Tamilnadu, India, to treat a variety of diseases, including dysmenorrhoea, leucorrhea, pre- and post-natal care, malaria, jaundice, gonorrhoea, wounds, cuts, boils, and skin disorders[17–20] The different ways these tribe members use A are listed in Table 2.

1.4. Terpenoids

The most prevalent terpenoid substances that may be separated from the aerial portions and roots of *A.paniculata*

Table 2: Uses of *Andrographis paniculata* in folk medicine

S. No	Therapeutic Uses	Mode of Uses
1.	Malaria	20 g of the whole plant is powdered, mixed in water, filtered, and given internally twice a day
2.	Eczema	2 g of powder is given internally once a day for 40 days
3.	Jaundice	10 g of water extract of the herb, heat treated by dropping hot sonte, given 3 times a day for 6 days
4.	Gonorrhea	2 g of the powder given internally or Plant juice is applied to the wounds
5.	Infected wounds	Paste of herb mixed with turmeric applied externally

are the diterpenoid lactones. The diterpenoids from *A.paniculata* have been recognised and isolated. The most prevalent and abundant is andrographolide. It is colourless and crystalline in appearance, and it tastes quite harsh. Gorter isolated it in its purest form for the first time in 1911. Deoxyandrographolide and neoandrographolide are among the other diterpenoids that have been identified mostly from the aerial sections of *A.paniculata.* Several researchers have isolated these diterpenoids. exhibited supplementary diterpenoids to the ones that are prominent. Unusual 23 carbon terpenoids that were identified from the plant's roots and aerial parts were among them.

1.5. Flavonoids

The main flavonoids that may be isolated from *A.paniculata* plant aerial parts, roots, and entire plant are called as flavones.[21] The flavonone 5, 7, 2', and 3'-tetramethoxyflavone can be found throughout the entire plant. A class of flavones known as 5-hydroxy-7, 2', 3'-trimethoxy flavones has been discovered to be present in entire plants.[22] A kind of flavone called 7-O-methyldihydrowogonin is present in the plant's root and aerial portion. The root, aerial portion, and entire plant have been shown to contain the flavone-1, 2'methylether type of flavone. Flavonoids of the type 5-hydroxy-7, 8, 2', and 5'-tetramethoxyflavone are present in whole plants.[23] Whole plants include a kind of flavone called dihydroskull capflavone.[24]

1.6. Miscellaneous compounds

Several miscellaneous compounds have been isolated, especially, from the roots of *A.paniculata.* Four xanthones were isolated from the roots using a combination of thin layer chromatography and column chromatography and were characterized by infrared radiation, mass, and nuclear magnetic resonance spectroscopic methods as 1, 8-dihydroxy-3,7-dimethoxy-xanthone, 4,8-dihydroxy 2,7-dimethoxy-xanthone, 1, 2-dihydroxy -6,8-dimethoxyxanthone and 3,7,8- trimethoxy-1-hydroxy-xanthone.[25] Five rare noriridoids designated as andrographolide A-E, along with curvifloruside were isolated from the roots of *A. paniculate.* Arabinogalactan proteins were isolated from the dried herbs.[26] Trace elements (Cr, Mn, Co, Ni, Zn, Cu, Se, Rb, Sr, and Pb) and macro-element (potassium and calcium) were identified and quantified in the roots. Cinnamic acid, caffeic acid, ferulic acid, and chlorogenic acid were also isolated from the whole plant.[27]

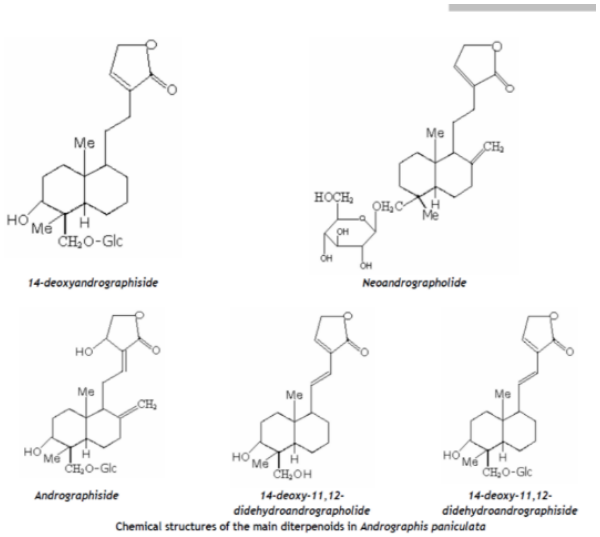

Fig. 2: Chemical structures of the mainditerpenoids in andrographis paniculata

2. Review on Anticancer Activity of A Paniculata

Andrographis paniculata (AP) is a potent immune system stimulator in two ways, according to studies done on mice: (1) antigen-specific immune response, in which antibodies are produced to fight off invading microbes, and (2) nonspecific immune response, in which macrophage cells scavenge and eliminate invaders. It is effective against a range of infectious and oncogenic (cancer-causing) pathogens since AP promotes both responses.[28] The early fascination with AP stemmed from both of its anti-cancer and hepatoprotective (liver-protecting) qualities. Like this, AP has a track record of successful treatment based on its immune-boosting processes. When cells ignore signals meant to stop their proliferation, cancer develops. Each step of normal cell growth involves the cells becoming more specialised to fulfil specific tasks. When cancer upsets normal development, cells do not mature; they more closely resemble immature body cells. The more they resemble immature cells, the more unfavorable the outcome: cancer grows and spreads (metastasizes) more rapidly. If a cancer cell can be made to mature (or differentiate), it will not have the ability to grow out of control. Researchers are

therefore searching for substances that can cause cancer cells to mature Researchers looked for naturally occurring chemicals that might change the direction of leukaemia cells in a mouse study. White blood cell cancer is known as leukaemia. The reason AP was chosen was because it contains terpenes, which were comparable to terpenes present in other plants and were known to stimulate cancer cells to differentiate. The study's findings showed that AP had strong leukaemia cell differentiation-inducing activity.[29] AP extracts from the plant's leaves are cytotoxic (cell-killing) against cancer cells in addition to maturing or differentiating cancer cells. This cancer cell-killing power was tested on lymphocytic leukaemia cells and human epidermoid carcinoma (squamous cell carcinoma) of the skin lining of the nasopharynx.[30] build the cellular apparatus It was the andrographolide component that was found to have the cancer cell-killing ability. This ability for killing cancer cells was superior to the levels of the effectiveness recommended by the National Cancer Institute for a cytotoxic substance. A group of Japanese researchers has reported that AP stopped stomach cancer cells from multiplying. After three days, there were less than 8 cancer cells growing in the presence of AP while the untreated cancer cells numbered 120. Another group of Japanese researchers tested AP on sarcoma cells.[31] These usually very malignant cancers affect muscle, connective tissue, and bones Under the microscope, it was discovered that AP inhibits the development of the malignancies.[32] In Buffalo, New York, experiments in the lab revealed that AP reduced the growth of human breast cancer cells at levels comparable to tamoxifen. Compared to most chemotherapeutic drugs used to treat cancer, extracts of AP are far less toxic. Although further research is required to pinpoint precisely which cancer types respond to AP, the preliminary findings are encouraging.[33] In 1977, AP was used in clinical research including 60 skin cancer patients, 41 of whom had definite metastases (the cancer was spreading). Twelve patients who were administered AP and its components exclusively recovered, according to a paper in the Journal of Chinese Medicine. Every other patient. Based on this report, American investigators obtained investigational new drug status from the FDA to test AP extract.[34] In 1996, early trials showed that the extract safely and effectively blocked growth of prostate and breast cancer, as well as non-Hodgkin's lymphomas.[35] Researchers think that AP likely prevents the manufacture of DNA in cancer cells based on the findings of employing AP on breast cancer cells that had been produced in a lab.[36] In the book Miracle Herbs by Stephen Holt, M.D., more information on cancer trials is provided. The anti-prostate cancer benefits of AP extract are comparable to those of the widely used and exceedingly toxic medication cisplatin, but without the toxicity, according to cancer trials.[37] A study evaluated the methanolic extract of Andrographis paniculate plant anticancer and immunomodulatory effectiveness in human cancer and immune cells. Before being examined for bioactivity, the methanolic extract of *Andrographis paniculata* was divided into dichloromethane, petroleum ether, and aqueous extracts.[38] The dichloromethane fraction of the methanolic extract still has the active components that are responsible for its anticancer and immunostimulatory properties, the results show. At low concentrations, the dichloromethane fraction increases the proliferation of human peripheral blood lymphocytes (HPBLs) while drastically inhibiting the growth of HT-29 (colon cancer) cells. Three diterpene compounds were recovered after further separation of the dichloromethane extract: andrographolide, 14-deoxyandrographolide, and 14-deoxy11,12didehydroandrographolide. On a variety of cancer cells representing different types of human malignancies, andrographolide demonstrated anticancer efficacy. Whereas in HPBLs, all three compounds demonstrated increased proliferation and IL-2 induction.[39] Different human cancer cell lines were grown in full media with and without test substances for 48 hours to assess the percentage growth using the SRB method. Percentage growth of the treated cells was calculated compared to the control untreated cells and the concentration required to inhibit the 50% growth (GI50 concentration. The numbers are the micromolar concentrations of the GI50 values. Andrographolide, one of the three compounds that were identified, with GI50 values that ranged from 10 to 28 M, inhibiting the growth of cancer cells.[40] 14-Deoxyandrographolide did not suppress the proliferation of other cancer cells but did moderately slow NCI/ADR-RES and A498 cell growth. No cancer cell line tested exhibited any inhibition of proliferation by 14-deoxy-11,12-didehydroandrographolide.[41] These findings indicate that andrographolide is the predominant contributor to the plant extract's anticancer action, with the other two components making a negligible contribution.[42] It was was elaborated on the cytotoxic action of andrographolide against KB (human epidermoid cancer) and P388 (lympholeukemiakaemia) cells, reported similar findings.[43] The growth inhibitory and differentiating activity of the methanol extract of aerial parts of *Andrographis paniculata* and some of the isolated compounds on M1 (mouse myeloid leukaemia) cells was also reported.[44] From above results it is evident that the major constituent andrographolide shows anticancer and immunostimulatory activities. The hollow fibre assay was performed in immunocompetent Swiss albino mice, and the in vivo results showed that andrographolide greatly inhibited the multiplication of cancer cells without manifesting any signs of toxicity in animals even at high dosages.[45] Although 14-deoxy11,12-didehydroandrographolide and 14-deoxy andrographolide did not exhibit any objective in vivo anticancer activity, studies are currently being conducted to determine whether

the immunostimulatory activity of these compounds that was seen in vitro will result in any objective in vivo anticancer activity through stimulation of the host immune system in terms of inhibiting tumour growth, preventing metastasis, and lengthening survival time[46,47] In a study it is reported that andrographolide in comparison to other two diterpenoids, deoxyandrographolide and neoandrographolide, had more potent anti-cancer activity against human leukemia HL-60 cells and other cancer cells. As demonstrated by chromosomal DNA fragmentation, accumulation of HL-60 cells in the sub-G1 cell cycle stage, the disappearance of mitochondrial cytochrome c and an increased expression of Bax and downregulation of Bcl-2 in the inhibited cells, it induced apoptosis of HL-60 cells.[48] In an investigation into the cytotoxicity of andrographolide to HepG2 human hepatoma cells revealed that the presence of andrographolide inhibited the development of HepG2 cells with an IC50 of 40.2 M after 48 hours of treatment. Andrographolide caused the cells to experience a late apoptosis and cell cycle arrest at the G2/M phase, according to a DNA fragmentation assay and flow cytometric analysis.[49] Cell cycle arrest was accompanied by a collapse in mitochondrial membrane potential (MMP), an increase in intracellular hydrogen peroxide (H2O2), a decrease in superoxide radicals (O2.-), and reduced glutathione. In the treated cells, p53, the gene's transcriptional regulator, and Bax expression were both increased, but not those of other apoptotic proteins like Bad, Bcl-2, orAlthough the presence of andrographolide also increased the activity of caspase-3, which directly affects apoptosis, HepG2 cell death could not be stopped by either a specific inhibitor of capsase-3 or the pan-caspase inhibitor VAD (Val-Ala-Asp), indicating that it was a caspase-independent cell death.[50]

3. Conclusion

Traditional medicine has made substantial use of *A.paniculata.* The main phytochemical components found in *A.paniculata* plant's aerial parts are flavonoids and diterpenoid lactones. The roots have been used to separate a variety of chemicals, including xanthones, uncommon noriridoids, macro and trace elements. This plant has been used to make a variety of formulations, extracts, and pure compounds that have been shown to have antimicrobial, anti-inflammatory, antioxidant, antidiabetic, cytotoxic, immune modulatory, phermones modulatory, modulatory of liver enzymes, antimalarial, neuroprotective, anticancer, antipyretic, antiplatelet, and hepatorenal protective activities. The bitter molecule andrographolide, which has the most promising biological actions, is one of the diterpenoid lactones. This paper offers a thorough description of the pharmacology, therapeutic applications, and phytochemistry of *A.paniculata.* To further guarantee its safety and acceptability as a source of contemporary medicine, clinical and laboratory investigations on the toxicity of plant extracts and other pure phytochemicals separated are crucial.

4. Source of Funding

None.

5. Conflict of Interest

None.

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