International Journal of Pharmacognosy and Life Science

E-ISSN: 2707-2835
P-ISSN: 2707-2827
www.pharmacognosyjournal.com
IJPLS 2023; 4(2): 111-119
Received: 09-07-2023
Accepted: 16-08-2023

Satruhan
Department of Botany, Guru Ghasidas Vishwavidyalaya, (A Central University), Bilaspur, Chhattisgarh, India

DK Patel
Department of Botany, Guru Ghasidas Vishwavidyalaya, (A Central University), Bilaspur, Chhattisgarh, India

Corresponding Author:
Satruhan
Department of Botany, Guru Ghasidas Vishwavidyalaya, (A Central University), Bilaspur, Chhattisgarh, India

Andrographis paniculata (Burm. F.) Wall Ex. Nees: A Review on their active components and medicinal properties

Satruhan and DK Patel

DOI: https://doi.org/10.33545/27072827.2023.v4.i2b.96

Abstract
The Acanthaceae family includes the bitter plant *Andrographis paniculata* (Burm. F.) Wall. Ex. Nees, widely known as Kalmegh or the "King of Bitters." It is native to India and Sri Lanka and is a tropical south-east Asian herb. One of the most widely utilised potential therapeutic plants in the world is *Andrographis paniculata*. This plant is traditionally used as an antioxidant, a liver and cardiovascular health tonic, and a remedy for the common cold, diarrhoea, fever from various infectious causes, and jaundice. Additionally, it is employed as a contraceptive and to treat sexual dysfunctions.
According to pharmacological and clinical investigations, *Andrographis paniculata* exhibits anti-inflammatory, antiallergenic, immunostimulatory, antiviral, antioxidant, hepatoprotective, cardiovascular, and other effects. The presence of active compounds like andrographolide, neoandrographolide, and kalmeghnin, which are derivatives of diterpenoids, is what gives this plant its medical significance. This review outlines the most recent scientific results and identifies areas in need of additional study.

Keywords: Acanthaceae, *Andrographis paniculata*, andrographolide, *Kalmegh*, medicinal plant

Introduction
The Acanthaceae family's significant medicinal plant, *Andrographis paniculata* Nees (Burm. F.) Wall. Ex Nees, also known as Kalmegh, King of Bitters, Bhui-neem, Maha-tita, Bhunimba, or Hara Chirayata, is extensively spread in India's plains. Only a few of the 28 species of small annual plants in the Andrographis genus, the most well-known of which is *Andrographis paniculata*, have any therapeutic significance. They are primarily found in tropical Asia.
It is an upright annual herb that tastes incredibly bitter across the entire plant. It has been utilised as a remedy for millennia in many different traditional medical systems around the world. In at least 26 Ayurvedic compositions, it is one of the most frequently utilised plants in India. The plant's panchang, which consists of five parts-the stem, leaf, flower, seed, and root-is utilised in a variety of Indian medical formulations.
The herb has stomachic, laxative, antipyretic, anti-inflammatory, expectorant, bitter, acrid, and cooling properties. Because andrographolide, a diterpene lactone, is present in Kalmegh, it is the primary bitter component in that herb.
The therapeutic benefits of Kalmegh are a result of its enzyme-induction-based mechanism of action. It is a key herb with anti-cold properties that is also used for fevers and to remove toxins from the body. It is used to treat a number of chronic and infectious diseases, including hepatitis, fever, herpes, sore throat, upper respiratory infections, and a variety of other chronic and infectious diseases. It has antibacterial, antimalarial, filaricidal, antidiarrheal, cardiovascular, effects on fertility, and liver and gallbladder protective properties.
The plant, as well as its isomers, such as andrographolide, neoandrograholide, dehydroandrographolide, and isoandrographolide, etc., are said to have anti-inflammatory, hepatoprotective, astringent, anodyne, tonic, alexipharmic, and anti-pyretic effects. They also aid in stopping the progression of piles, gonorrhoea, bronchitis, diabetes, and cholera.
Plant flavonoids demonstrated strong prevention of platelet aggregation caused by collagen, arachidonic acid, thrombin, and platelet-activating factor.

Furthermore, in isolated rat thoracic aorta, a diterpenoid showed a mild vasorelaxing action. The plant is a key component in many pharmaceutical formulations sold on the domestic and foreign markets.

The *Andrographis paniculata* intended benefits must be carefully considered because it is employed in traditional medical systems to treat a wide range of illnesses. As a result, this research examines the ethnobotany, phytoconstituent characterisation, and pharmacological characteristics of AP. Additionally, consideration is given to the chemical composition, biological processes, and potential mechanisms of action of phytoconstituents.

Andrographis paniculata, "King of Bitters," "Kalmegh," "Hempedu bumi," and "Andrographolide" were among the search terms utilised. The list of references for all available publications was used to search the databases indicated above for further pertinent papers. We provided a list of some subjects that require more research and briefly highlighted recent scientific discoveries.

Fig 1: *Andrographis paniculata* (Picture courtesy by Author)

Table 1: Taxonomical Classification

Kingdom:	Plantae, Plants;
Sub-kingdom:	Tracheobionta, Vascular plants;
Super division:	Spermatophyta, Seed plants;
Division:	Angiosperma
Class:	Dicotyledonae
Subclass:	Gamopetalae
Series:	Bicarpellate
Order:	Personales
Tribe:	Justicieae
Family:	Acanthaceae
Genus:	*Andrographis*
Species:	*Paniculata*

Distribution and botanical description

The tropical Asian nations of Sri Lanka, India, Thailand, Peninsular Malaysia, and Indonesia all have distributions of *Andrographis paniculata*. Plant-native populations can be found all over Sri Lanka and South India, which may be the origin and diversity of the species. Madhya Pradesh, Chhattisgarh, Orissa, Maharashtra, Assam, West Bengal, Uttar Pradesh, Tamil Nadu, Karnataka, and Kerala are among the Indian states where it is present.

There are many different environments where *Andrographis paniculata* can be found, including plains, hill slopes, wastelands, farms, dry or wet regions, sea coasts, and even roadsides. The plant needs warm, muggy weather with lots of sunlight. After the monsoon season begins, the plant develops luxuriantly and begins to bloom in September. Up until the temperature drops in December, blooms and fruits continue in northern India. In 90-105 days, the maximum amount of herb biomass can be harvested before the leaves begin to shed. Winter does not affect the crop, and the second year's ratoon crop produces higher biomass.

When the active ingredient andrographolide is abundant in the leaves during the stage of flower initiation harvesting should be done. Since the entire plant retains the active ingredient, the entire harvest is dried in the shade and ground into powder. Dried herb yields of 3.5-4.0 tonnes/ha are produced by well-maintained crops planted throughout the monsoon season. The bitter annual herb *Andrographis paniculata* is erect grows 0.3-1.0 m tall, and has a quadrangular, heavily branching stem. Simple, opposite, lanceolate leaves with short petioles measure 3–7 cm long and 1-2.3 cm wide. They are glabrous with a slightly undulating edge and an acuminate apex with a tapering base. Small, solitary flowers with hairy corollas grow in panicles and are either white or pale pink in colour. There are numerous subquadrate, yellowish-brown seeds inside erect, linear, or oblong capsules.

The common name for the species is Quasabhuva in Arabic, Kalmegh in Bengali, The Creat, King of Bitters in English, Gujarati, Hindi, Kirayat, Nelaberu in Kannada, Oli-kiryata in Malayalam, Bhuinimba in Oriya, Naine-havandi in Persian, Nilavembu in Tamil, and Nilavembu in Telugu.

Table 2: The Morphology of *Andrographis paniculata*

Traits	Values/Characteristics
Plant height	30-110 cm
Stem	Dark green
Length	30-100 cm
Diameter	2-6 mm
Shape	Quadrangular with longitudinal furrows and wings on the angles of the young parts, slightly enlarged at the nodes
Leaves	Glabrous
Length	2-12 cm
Width	1-3 cm Arrangement Lanceolate Shape Pinnate, acute apex, entire margin Flowers White with rose-purple spots on the petals
Size	Small, in lax spreading axillary and terminal racemes or panicles
Seed	Capsules linear-oblong, acute at both ends
Size	1.9 cm × 0.3 cm Colour Yellowish brown Shape Subquadrate, numerous
Flowering and fruiting	December to April

Agricultural technique

Seed culture is a common way for plants to reproduce. Farm yield has been affected by planting and harvesting times. When in question, plant *Andrographis paniculata* seeds isolate 30 *15 cm between May and July to achieve a plant thickness of 222 thousand plants. Regardless, seed torpidity is mechanically important for *Andrographis paniculata* improvement. However, hormones media and high-temperature water treatment have been suggested as solutions to this problem. Because of changeability among seed-determined descendants and inadequate and delayed seedling establishment, this method is insufficient to meet the market amounts needed. As a result, non-traditional spread methods, such as plant tissue culture procedures, are optional techniques for delivering a large number of

plantlets in a short period of time and increasing phytochemical content in *Andrographis paniculata*. Tissue culture systems have been used to induce massive *Andrographis paniculata* extension. According to researchers, *in vitro*-recovered *Andrographis paniculata* contains a higher proportion of andrographolide and appears differently than mother plants. The suspension social orders of *Andrographis paniculata* can be used to optimize the ideal formation of andrographolide in a limited capacity to the middle. Plant tissue culture has also been active in producing new flavones from callus culture.

Materials and Methods

On the current literature, searches were carried out in the widely used scientific databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Science Direct (http://www.sciencedirect.com/), Scopus (http://www.scopus.com/), Web of Science (http://webofknowledge.com), Springer Link (http://link.springer.com/), Wiley Online Library (http://onlinelibrary.wiley.com/), and advance search in Google.

Used plant parts

The plant's aerial parts (leaves and stems), which are used for their therapeutic value, are used to extract the active phytochemicals. Roots are also utilised very infrequently.

Ethnobotanical utilization

According to ethnobotany, AP's leaves and roots have been used for ages in Asia and Europe to treat a wide range of medical conditions. But there are some restricted uses for the entire plant as well. It is advised to use this remedy to remove toxins from the body and to reduce body heat in cases of fever due to its "cool property" activity.

Due to their powerful "blood cleansing" capabilities, the plants are also advised for usage in cases of leprosy, gonorrhoea, scabies, boils, skin eruptions, and chronic and seasonal fever. There is a list of the general traditional uses of AP in various traditional medical systems (TMS) or nations. Additionally, it is frequently utilised as a folk cure in several nations by traditional healers, tribes, or communities for therapeutic purposes.

Phytochemical ingredients

There are numerous applications for the aerial portions of *Andrographis paniculata.* About the part used, geography, season, and time of harvest, among other factors, there are significant variations in the phytochemical content. Just before the flowering season (after 90 days), andrographolides are in high concentrations, which thereafter progressively decline. The amount of readily available diterpene lactones, of which andrographolide is the main one contributing to pharmacological activity, is highest in the aerial portions (leaves and stems) and lowest in the roots. The additional lactones include andrographon, andragraphan, deoxyandrographolide, andrographiside, andrographosterol, as well as 14-deoxy-11-andrographolide, 14-deoxyandrographolide, neoandrographolide, 14-deoxy-11, 12 didehydroandrographolide, and 14-deoxyandrographolide, etc.

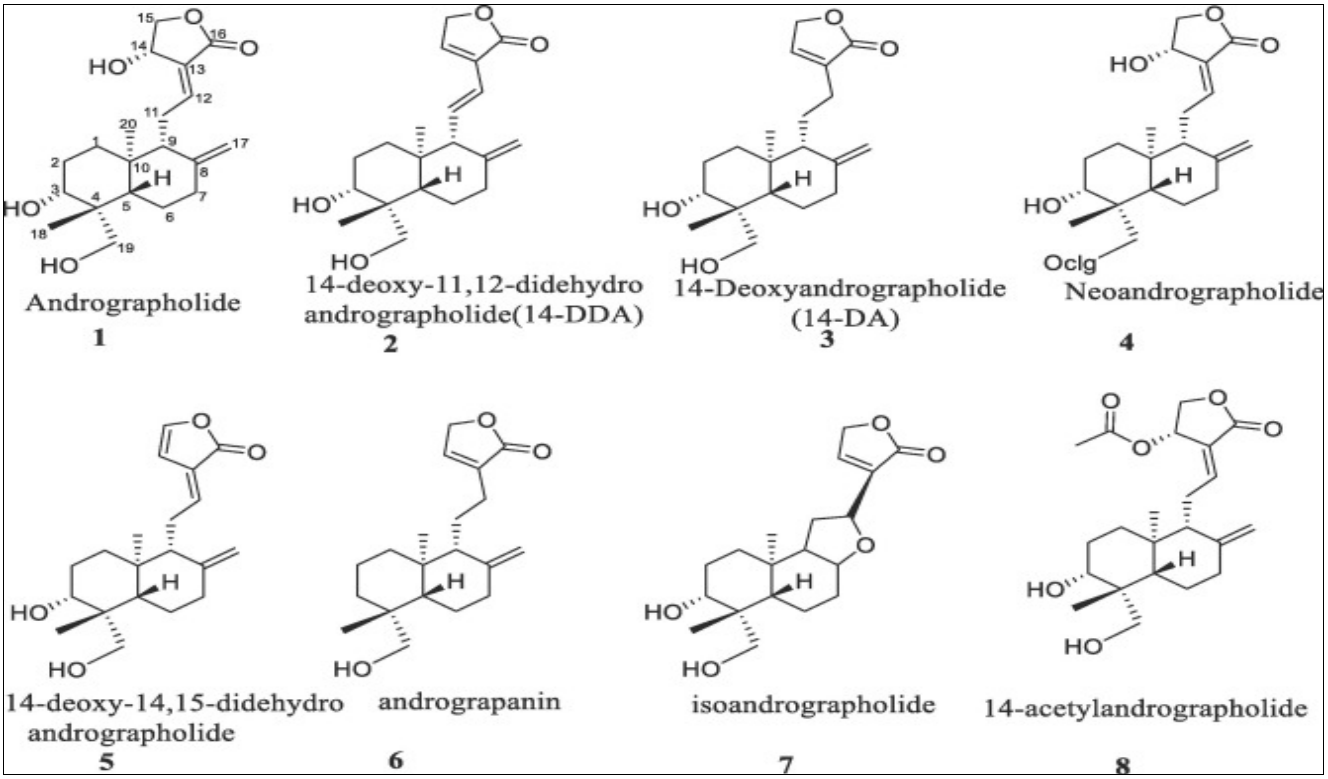
It is important to note that many of *Andrographis paniculata's* active ingredients belong to the ent labdane class and appear alongside certain flavonoids. Minor components of *Andrographis paniculata* also include xanthones (only roots) and derivatives of quinoc acid. This article mentions a handful of the reported works on phytochemistry. In addition to previously recognised substances, a new series of six ent-labdane diterpenoids, two diterpene glucosides, and four diterpene dimers were discovered in a study by Matsuda *et al*. (1994) [57] on the ethyl acetate fraction of a methanol extract of *Andrographis paniculata.*

They have been discovered to be effective cell differentiation inducers and could be used to treat cancer. Reddy *et al*. (2003) [58] reported the isolation of five known flavonoids (7-Omethyldihydrowogonin, 7-Omethylwogonin, skullcapflavone I 20 -methyl ether, 7-O-methylwogonin 5-O-glucoside, and skullcapflavone I 20 -O-glucoside) and four known diterpenoids. The flavone isolated was 5-hydroxy-70, 20, 60 -trimeth (14-deoxy-11, 12-didehydroandrographolide, andrographolide, isoandrographolide and neoandrographolide).

5-hydroxy-7, 20, 30-trimethoxyflavanone and 5, 7, 20, 30-tetramethoxyflavanone were discovered and identified by Rao *et al*. in 2004. In addition to four known labdane type diterpenoids (14-deoxy11, 12-didehydroandrographolide, andrographolide, isoandrographolide, and neoandrographolide) and five known flavonoids (7-Omethyldihydrowogonin, 7-O-methylwogonin, skullcapflavone I 20-methyl ether, 7-O-methylwogonin 5-O-glucoside

In addition to seven others known diterpenoids, Pramanick *et al*. (2006) [59] reported the isolation of a new labdane type diterpenoid, andropanolide, from the leaves of *Andrographis paniculata* (andrographolide, andrograpanin, isoandrographolide, 14-deoxy-11, 12 didehydroandrographolide, 14deoxyandrographolide, isoandrographolide, neoandrographolide). Two human cancer cell lines were discovered to be cytotoxic to two novel diterpenes, andrographolactone and andrographolactone, after these compounds were extracted from the aerial regions of ethanolic extracts.

From the ethanol extract of the leaves of *Andrographis paniculata*, which has a cis-diol group in the lactone moiety, Wang *et al*. (2009) [60] and recently Xu *et al*. (2010) reported the yield of one novel diterpene (13R, 14R) 3, 13, 14, 19-tetrahydroxy-ent-labda-8, 11-dien-16, 15-olide and three other known diterpenoids (andrographolide, neoandrographolide, andrograpanin, 14deoxyandrographolide, 14-deoxy-11,12-didehydroandrographolide, 14-deoxyandrographoside, andrographoside and 8-methylandrographolide).



https://ars.els-cdn.com/content/image/1-s2.0-S0045206819312994-gr1.jpg

Fig 1: Compounds found in the leaves of *Andrographis paniculata*

Pharmacological Activity

Studies done in previous decades have shown that Andrographis when used properly, has a wide variety of pharmacological effects, some of which are quite advantageous

- **Vermicidal (kills intestinal worms):** All women are advised to avoid using it while pregnant out of caution even though Ayurvedic tradition permits it to be used for brief periods during pregnancy. Andrographis is remarkably non-toxic in practically all other aspects. (Hot: in this instance, mildly ruffling the skin.
- **Analgesic (pain killer):** Decreases inflammation and capillary exudation, with the anti-inflammatory effect likely being partially mediated by adrenal function) (fights bacterial activity; although Andrographis appears to have weak direct antibacterial action, it has a remarkably beneficial effect in reducing diarrhoea and symptoms arising from bacterial infections.
- **Antiperiodic:** Combats periodic/intermittent illnesses like malaria.
- **Antipyretic:** Fever.
- **Antithrombotic:** A blood clot inhibitor.
- **Antiviral:** Suppresses viral activity.
- **Cardioprotective:** Safeguards heart muscles.
- **Choleretic:** Changes the characteristics and movement of bile.
- **Depurative:** The blood in particular, is cleaned and made pure.
- **Digestive:** Increases digestion
- **Expectorant:** Encourages the release of mucus from the respiratory system.
- **Hepatoprotective:** Safeguards the gallbladder and liver.
- **Hypoglycemic:** Lowers blood sugar.
- **Immune Enhancement:** Enhances CD4 + and T lymphocyte numbers, suppresses HIV-1 replication, and promotes white cell phagocytosis.
- **Laxative:** Helps with bowel elimination.
- **Sedative:** Natural sedatives like valerian root, hops, skullcap, etc. are recognised as having the same effect as the calming plant chamomile.
- **Thrombolytic:** Anti-clotting agent

Liver-protective behaviour

The traditional Indian medical system makes considerable use of the hepatoprotective and stimulatory properties of *Andrographis paniculata* (Kalmegh). This plant's leaves provide an aqueous extract that has long been used to treat jaundice and a variety of liver conditions. There are roughly 26 distinct treatments, including *Andrographis paniculata*, utilised in conventional ayurveda therapy to treat liver diseases. The major ingredient in *Andrographis paniculata*, andrographolide, was discovered to be successful in reducing liver damage brought on by carbon tetrachloride.

A notable hepatoprotective effect is also demonstrated by andrographolide against various forms of liver damage brought on by paracetamol or galactosamine, and it outperformed the traditional antioxidant silymarin in avoiding a drop in bile output brought on by paracetamol. It also had a significant hepatoprotective effect by lowering the formation of the lipid peroxidation product malondialdehyde (MDA), which revealed the diterpene lactones in andrographolide's capacity to scavenge free radicals, as well as by maintaining high levels of glutathione, glutamic pyruvate transaminase, and alkaline phosphatase in mice treated with carbon tetrachloride

Andrographolide was found to be antihepatotoxic when used to treat mastomys natalensis for hepatic damage brought on by Plasmodium berghei K173. In conscious rats and anaesthetic guinea pigs, andrographolide significantly increased bile flow, bile salt, and bile acid, suggesting that it may be a robust activator of gall bladder function. After

receiving ongoing treatment with *Andrographis paniculata*, the majority of patients with infective hepatitis showed definite improvement, including an increase in appetite and liver function tests, regular recovery from jaundice, and a decrease in fever.

Cold-related prevention

A number of clinical studies have been done to prove that andrographolide isolated from Kalmegh has a protective effect against the common cold. In a controlled study, andrographolide was also found to have a beneficial effect on tiredness, shivering, sore throat, muscular ache, rhinitis, sinus pains and overall disease. The inhibitory activity of andrographolide against the common cold may be due to its immuno-stimulant effect. As a preventive for the common cold, studies showed that andrographolide may increase the body's resistance to infection by stimulating the production of antibodies and large white blood cells that scavenge foreign matter.

Antipyretic effect

A number of clinical studies have been done to prove that andrographolide isolated from Kalmegh has a protective effect against the common cold. In a controlled study, andrographolide was also found to have a beneficial effect on tiredness, shivering, sore throat, muscular ache, rhinitis, sinus pains and overall disease. The inhibitory activity of andrographolide against the common cold may be due to its immuno-stimulant effect. As a preventive for the common cold, studies showed that andrographolide may increase the body's resistance to infection by stimulating the production of antibodies and large white blood cells that scavenge foreign matter.

Anti-allergy action

The herb *Andrographis paniculata* is used to treat allergic reactions as well as skin-related issues. Previous studies have backed its usage in the management of dermatological conditions. According to a study by Gupta *et al*. in 1998, the active ingredients of *Andrographis paniculata*, andrographolide and neoandrographolide, have anti-allergic properties.

In rats, the compounds were examined for their ability to prevent PCA and stabilise mast cells. Both andrographolide and neoandrographolide were seen to strongly reduce PCA in a dose-dependent manner. They also dramatically reduced the degranulation of mast cells brought on by compound 48/80 or egg albumin. Andrographolide's ability to stabilise mast cells appears to be the mechanism behind its anti-allergic action.

Anti-diarrheal properties

It has been demonstrated that *Andrographis paniculata* extracts exhibit antidiarrheal action in E. coli-contaminated diarrhoea. The most widely used antidiarrheal medication, loperamide, and andrographolide is shown similar activity. It has been demonstrated in various clinical investigations that andrographolide significantly reduces bacterial diarrhoea and dysentery in patients, which may be related to the molecule's antibacterial activity.

Antivenomous Behaviour

Mice experimentally injected with rattlesnake venom s.c. injection (2.5-15 mg/kg body weight) responded favourably to oral administration of plant extracts of *Andrographis paniculata* (7.2 mg/kg body weight) and purified fractions (2.4 mg/kg body weight) (Rattlesnake). *In vitro* as opposed to *in vivo*, the separated fractions efficiently reduced the harmful effect of rattlesnake venom.

Malaria prevention

Malaria is one of the oldest recorded diseases in history. Every year, malaria claims a significant number of lives. In many endemic regions of the world, its medication resistance has led to treatment failures. There is an urgent need for new and well-tolerated antimalarial pharmaceuticals for both prophylaxis and treatment of malaria due to the challenges in developing effective vaccinations as well as the negative side effects of the currently available antimalarial medications.

Curcumin and andrographolide exhibit strong antiplasmodial efficacy against Plasmodium falciparum erythrocytic stages *in vitro* and against Plasmodium berghei ANKA strains in mice. According to docking study data, andrographolide might be a protease inhibitor for malaria parasites.

Immunosuppressive behaviour

Purified andrographolides (1 mg/kg body weight) or an ethanol extract of the aerial portions (25 mg/kg body weight) administered intragastrically to mice enhanced the formation of antibodies and the delayed-type hypersensitivity reaction to sheep red blood cells. Additionally, the extract induced a non-specific immunological response in mice as evidenced by the proliferation of splenic lymphocytes, the macrophage movement index, and the phagocytosis of [14C] leucine-labeled E. coli. The fact that the extract outperformed andrographolide and neoandrographolide by themselves suggests that additional components might be involved in the immunostimulant response.

Action against bacteria

Staphylococcus aureus and Escherichia coli growth *in vitro* was reduced by an ethanol extract of the leaves. Proteus vulgaris' *in vitro* growth was reduced by a 50% methanol extract of the leaves. When dried powder from the aerial portions was tested against E. coli, Staphylococcus aureus, Salmonella typhi, or Shigella species, no *in vitro* antibacterial activity was found.

Anti-viral behaviour

At viricidal concentrations, andrographolide, neoandrographolide, and 14-deoxy11, 12-didehydroandrographolide are claimed to be viricidal against the herpes simplex virus type 1 (HSV-1) with minimal damage.

Anti-oxidant function

In an investigation, Trivedi *et al*. (2001) [61] evaluated the effects of Benzene hexa chloride and Kalmegh on antioxidant activity in mice. They used the enzymes glutamyl transpeptidase, glutathione-stransferase, and lipid peroxidation (BHC). Following the BHC action, the activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione levels were reduced. Neoandrographolide was isolated from Kalmegh, and Kamdem *et al*. discovered the chemical mechanism

underlying its superoxide scavenging activity in an experiment in 2002.

Neoandrographolide was thought to be able to donate the allylic hydrogen of the unsaturated lactone ring to free radicals, scavenging them. The ratio of the reaction between neoandrographolide and the superoxide radical produced by KO2 in DMSO was discovered to be 2: 1. A diacid generated by the opening of the lactone ring was found to be one of the main reaction products.

Neoandrographolide's antiradical activity was preceded by hydrogen abstraction from carbon C-15. According to Sheeja *et al* 2007 [62].'s study, the methanolic extract of Kalmegh was successful in preventing the production of oxygen-derived free radicals such as superoxide (32%) and hydroxyl radicals (80%), as well as lipid peroxidation (80%) and nitric oxide (42.8%), in an *in vitro* system.

Effects of infertility

Both antifertility and pregnancy-terminating effects of AP are evident. It is advised to use AP just temporarily in India, where it is used to treat common conditions like diarrhoea, fever, and other digestive issues. This is because the chemicals have natural contraceptive properties. Studies on male rats were conducted to ascertain the precise impact on fertility.

According to one study, the formation and maturation of sperm cells, or spermatogenesis, was inhibited when AP was administered as dry leaf powder (105 mg powder/kg body weight) daily for 60 days (61). The authors hypothesised that the plant has antispermatogenic or antiandrogenic properties, which prevent the effects of androgens. It should be mentioned that many herbal extracts have an impact on reproductive processes and shouldn't be consumed while pregnant because of this. Studies by Zoha and associates, also in India, revealed impacts on female mice's infertility (62). After mating (five times) with known fertile males who did not receive the AP, none of the rats given 2 gm/kg body weight of sun-dried AP powder daily for six weeks became pregnant.

When paired with similar males, the mice who did not get the AP produced normal litters. Ovulation may have been prevented as a result of AP. Scientists were inspired to conduct this research because Bangladesh, where the plant is widely accessible, may be able to employ it as an antifertility agent. Studies in human placental tissue in culture revealed that andrographolide sodium succinate (derived from AP) was efficient in reducing the production of human progesterone (46). This hormone is essential for a healthy pregnancy.

The AP utilised had a tissue-specific effect, meaning it only had an impact on the tissues for which it was designed. Even at the highest studied levels, there were no negative impacts on other normal human tissue. The compounds seemed like promising contraceptives, according to the researchers. Dehydroandrographolide was used in additional tests on female mice, and the results showed that the dose needed to affect pregnancy was 250 mg/kg body weight. In neither the 105 mg/kg body weight dose of AP nor the 2g (2,000 mg/kg body weight) dose administered to the female animals in the tests mentioned above would this amount of pure substance be present. Therefore, it seems improbable that the active ingredient in AP that causes infertility is a molecule from the andrographolide family.

Andrographolide induces G1/G0 Cell Cycle Arrest

Cyclin and cyclin-dependent kinases (CDK) are the two subunits of the protein series involved in cell cycle progression, in which cyclin is the regulatory component, and CDK is the catalytic subunit. CDKs are the regulators of cell cycle checkpoints. Among these CDK4 and CDK6 are the targets of anticancer drugs since they regulate the cell cycle progression at the G1 restriction point. The p27 and p21 are proteins that hurt cell proliferation. It inhibits the activities of cyclin E/CDK2 and cyclin A/CDK2, and they seem to activate cyclin D/CDK complexes. In proliferating cells, p27 is prevalently bound to cyclin D/CDKs, whereas, in G1-arrested cells, p27 is found in complexes with cyclin E/CDK2. Breast cancer develops due to the uncontrolled proliferation of breast epithelial cells. Loss of function of the p27 gene is one of the reasons for breast cancer. The p27 gene is located in the human chromosome 12p 13th locus. Biallelic mutation of the p27 gene is rare in the case of breast carcinoma. The p27 protein levels are high in quiescent cells and undetectable or very low in proliferative cells. The p27 mRNA seems to be constant throughout the cell cycle, but the p27 protein level is high in the G1 phase and decreases during the end of the G1 phase. During the end of the G1 phase, the p27 protein is degraded via the ubiquitin-proteasome pathway. The human ubiquitin-conjugating enzymes are Ubc2, and Ubc3, specifically involved in the ubiquitination of p27. Breast cancer patients with a low expression of p27 have a high mortality rate than patients with have high expression of p27. Induction of p27 in breast carcinoma is an effective strategy for breast cancer treatment. Andrographolide blocks breast cancer cell proliferation via the induction of p27 and concomitant decrement in the levels of CDK4. Fluorescence-activated cell sorting (FACS) analysis and western blot analysis were conducted in MCF-7 breast cancer cell lines after treatment with andrographolide. FACS analysis showed that cells were arrested at the G0/G1 phase. Western blot analysis confirmed the observation of FACS analysis by detecting the presence of cell cycle inhibitor proteins p27. Induced p27 proteins bind with CDK4/ D1 complex and prevent the phosphorylation of retinoblastoma. This prevents the release of elongation factor and transcription of S phase proteins. Andrographolide showed a time- and concentration-dependent inhibitory effect on MDA-MB-231 breast cancer cell proliferation. The treatment did not affect normal breast epithelial cells, MCF10A (> 80%). The number of cells in S, as well as the G2/M phase, was increased after 36 hours of treatment. MDA-MB-231 cells exposed to andrographolide for 24 hours showed significant cell cycle arrest at the G2/M phase. Andrographolide also inhibits breast cancer growth via the inhibition of hypoxia-inducible factor-1 through the phosphatidylinositol 3-kinase/AKT pathway.

Cytotoxic and anti-tumor Activity

The inhibition of hepatoma tumor growth induced by andrographolide (10 mg/kg) was found in a xenograft mouse tumor model *in vivo*. The miRNA chip analysis showed an increased expression of 22 miRNAs, whereas the expression of other 10 miRNAs decreased after treatment. Functional annotation of the target genes based on the differentially expressed miRNAs suggested that the majority of the genes were involved in a variety of signalling

pathways, including miRNAs in cancer, mitogen-activated protein kinases (MAPKs) and focal adhesion. Yang *et al*. studied the cytotoxic effect of andrographolide on human T-ALL (T-cell acute lymphoblastic leukaemia) cells. It was found that a 10 μg/mL compound could significantly induce Jurkat cells' apoptosis, depending on the inhibition of the PI3K/ AKT pathway. Synergistic anticancer effects of andrographolide and paclitaxel (PTX) (widely used in chemotherapy for cancer treatment) were studied against A549 NSCLC (non-small cell lung cancer) cells. Andrographolide showed a time- and concentration-dependent inhibitory effect on highly proliferative MDA-MB-231 breast cancer cell proliferation, however, the treatment did not affect normal breast epithelial cells, MCF-10A (>80%). Increased production of reactive oxygen species (ROS) with a corresponding decrease in mitochondrial membrane potential (MMP), and externalization of phosphatidylserine was observed, while the population of apoptotic cells increased with prolonged exposure to andrographolide. Additionally, caspase-3 and caspase-9 were activated while Bax and Apaf-1 expression were significantly increased with a corresponding decrease in Bcl-2 and Bcl-xL expression in andrographolide-treated cells. Furthermore, andrographolide was also reported to inhibit prostate cancer cells (LNCaP, C4-2b, and PC), by targeting cell cycle regulators, CXCR3 and CXCR7 chemokine receptors. 14-Deoxy-11,12-didehydroandrographolide (14-DDA), a major diterpenoid of AP, induced the formation of endoplasmic reticulum (ER) vacuoles and autophagosomes, with concurrent upregulation of LC3- II in the breast carcinoma cells. The mechanism of action involved an increase in cytosolic calcium concentration leading to a collapse in mitochondrial membrane potential in LC3-II cells. The ER stress pathway was significantly upregulated, and DDIT3 knockdown suppressed the formation of both ER vacuoles and autophagosomes, indicating that 14-DDA-induced ER stress and autophagy are dependent on this transcription factor. The inhibitory effects of andrographolide on the growth of multiple myeloma (MM) cells and its possible impact on the nuclear factor (NF)-κB signalling pathway were studied by Gao and Wang.

Andrographolide to protect Cancer Patients from SARS-CoV-2 Infections

Recent studies had revealed the discovery of potential drugs by computational methods, which act as therapeutic targets for SARS-CoV-2 infection. The natural compound, 14-deoxy11, 12-didehydroandrographolide from *Andrographis paniculata* was found to be acting as a potential antiviral, anti-inflammation, and anti-tumor compound. The andrographolide derivative exhibited a relatively high binding affinity to the three target proteins, Nsp1, Nsp3c, and ORF7. Recent studies had also revealed neoandrographolide to be a potential TMPRSS2 inhibitor and, thus, predicted it also to act as an anti-virus natural compound. Herbal medicines containing andrographolide, neoandrographolide, and 14-deoxy-11, 12-didehydroandrographolide from *Andrographis paniculata* as major components might be meaningful for the treatment of SARS-CoV-2 infections.

Conclusion

Finally, it is clear from the extensive literature review and analysis of the experimental findings that *Andrographis paniculata* is a significant medicinal and industrial cash crop with enormous potential for the treatment of a wide range of illnesses and other conditions. A diterpenoid lactone with a variety of pharmacological properties that have been identified in traditional systems of medicine is andrographolide.

Along with its many other medical applications, andrographolide also has some adverse effects that are only noticeable after an overdose, such as nausea, vomiting, and appetite loss. Therefore, using herbal drug delivery technologies, researchers may continue to produce strong formulations of *Andrographis paniculata* and its isolated molecule, andrographolide.

References

1. Akbar S. *Andrographis paniculata*: a review of pharmacological activities and clinical effects. Altern Med Rev. 2011;16(1):66-77.
2. Akilandeswari G, Anand AV, Sampathkumar P, Moorthi PV, Preethi B. A Prospective Review on Phyto-Pharmacological Aspects of *Andrographis paniculata*. Syst Rev Pharm. 2019;10(1):15-19.
3. Bharati BD, Sharma PK, Kumar N, Dudhe R, Bansal V. Pharmacological activity of *Andrographis paniculata*: a brief review. Pharmacologyonline. 2011;2(1):10.
4. Bhattacharya S, Puri S, Jamwal A, Sharma S. Studies on seed germination and seedling growth in Kalmegh (*Andrographis paniculata* Wall. Ex Nees) under abiotic stress conditions. Int. J Sci Environ Technol. 2012;1(3):197-204.
5. Chao WW, Lin BF. Hepatoprotective diterpenoids isolated from *Andrographis paniculata*.
6. Chatterjee N, Biswas S, Saha NC, Biswas SJ. *Andrographis paniculata* a traditional herb with pharmacological properties: a review. Global J Res Med Plants & Indig Med. 2014;3(5):206.
7. Chauhan ES, Sharma K, Bist R. *Andrographis paniculata*: A review of its phytochemistry and pharmacological activities. Res J Pharm Tech. 2019;12(2):891-900.
8. Coon JT, Ernst E. *Andrographis paniculata* in the treatment of upper respiratory tract infections: a systematic review of safety and efficacy. Planta Med. 2004;70(04):293-298.
9. Dai Y, Chen SR, Chai L, Zhao J, Wang Y, Wang Y. Overview of pharmacological activities of *Andrographis paniculata* and its major compound andrographolide. Crit Rev Food Sci Nutr. 2019;59(sup1):S17-S29.
10. Das P, Srivastav AK. Phytochemical extraction and characterization of the leaves of *Andrographis paniculata* for its anti-bacterial, anti-oxidant, anti-pyretic and anti-diabetic activity. Int. J Innov Res Sci Eng Technol. 2014;3:15176-15184.
11. Hossain MD, Urbi Z, Sule A, Rahman KM. *Andrographis paniculata* (Burm. f.) Wall. ex Nees: a review of ethnobotany, phytochemistry, and pharmacology. Scientific World J; c2014.
12. Hossain S, Urbi Z, Karuniawati H, Mohiuddin RB, Moh Qrimida A, Allzrag AMM, *et al*. *Andrographis paniculata* (burm. F.) wall. Ex nees: an updated review of phytochemistry, antimicrobial pharmacology, and clinical safety and efficacy. Life. 2021;11(4):348.

13. Islam MT, Ali ES, Uddin SJ, Islam MA, Shaw S, Khan IN, *et al*. Andrographolide, a diterpene lactone from *Andrographis paniculata* and its therapeutic promises in cancer. Cancer Lett. 2018;420:129-145.
14. Jarukamjorn K, Nemoto N. Pharmacological aspects of *Andrographis paniculata* on health and its major diterpenoid constituent andrographolide. J Health Sci. 2008;54(4):370-381.
15. Joselin J, Jeeva S. *Andrographis paniculata*: A review of its traditional uses, phytochemistry and pharmacology. Medicinal & Aromatic Plants. 2014;3(4):1-16.
16. Joseph SM. Scientific aspects of the therapeutic use of *Andrographis paniculata* (Kalmegh): A review. Int J Pharm Sci Rev Res. 2014;27:10-16.
17. Kour N. *Andrographis paniculata*: A review on ethnomedicinal potential and biological activities. J Plant Dev Sci. 2016;8(1):1-6.
18. Kumar A, Dora J, Singh A, Tripathi R. A review on king of bitter (Kalmegh). Int. J Res Pharm Chem. 2012;2(1):116-24.
19. Kumar B, Verma SK, Singh HP. Effect of temperature on seed germination parameters in Kalmegh (*Andrographis paniculata* Wall. ex Nees.). Ind Crops Prod. 2011;34(1):1241-1244.
20. Kumar SS, Thoppil JE. Andrographolide a Potential Therapeutic Drug against Breast Cancer: A Review. Int J Pharmacogn Phytochem Res. 2020;12(2):72-77.
21. Li W, Xu X, Zhang H, Ma C, Fong H, van Breemen R, *et al*. Secondary metabolites from *Andrographis paniculata*. Chem Pharm Bull. 2007;55(3):455-458.
22. Liaqat H. *Andrographis paniculata*: A review of its anti-cancer potential. Med Aromat Plants (Los Angeles). 2021;10:384.
23. Maity GN, Maity P, Dasgupta A, Acharya K, Dalai S, Mondal S. Structural and antioxidant studies of a new arabinoxylan from green stem *Andrographis paniculata* (Kalmegh). Carbohydr Polym. 2019;212:297-303.
24. Malik Z, Parveen R, Parveen B, Zahiruddin S, Khan MA, Khan A, *et al*. Anticancer potential of andrographolide from *Andrographis paniculata* (Burm. f.) Nees and its mechanisms of action. J Ethnopharmacol. 2021;272:113936.
25. Meenatchisundaram S, Parameswari G, Subbraj T, Suganya T, Michael A. Medicinal and pharmacological activities of *Andrographis paniculata*–Review. Ethnobot Leaflets. 2009;13(1):55-58.
26. Mehta S, Sharma AK, Singh RK. Ethnobotany, pharmacological activities and bioavailability studies on King of Bitters (Kalmegh): a review (2010-2020). Combinatorial Chemistry & High Throughput Screening. 2022;25(5):788-807.
27. Mishra SK, Sangwan NS, Sangwan RS. Phcog rev.: Plant review *Andrographis paniculata* (Kalmegh): A review. Pharmacognosy Reviews. 2007;1(2):283-298.
28. Misra P, Pal NL, Guru PY, Katiyar JC, Srivastava V, Tandon JS. Antimalarial activity of *Andrographis paniculata* (Kalmegh) against Plasmodium berghei NK 65 in Mastomys natalensis. International Journal of Pharmacognosy. 1992;30(4):263-274.
29. Murthy HN, Park SY, Paek KY. Domestication of *Andrographis paniculata* (King of Bitters). Medicinal Plants. 2021:55-68.
30. Mussard E, Cesaro A, Lespessailles E, Legrain B, Berteina-Raboin S, Toumi H. Andrographolide, a natural antioxidant: an update. Antioxidants. 2019;8(12):571.
31. Niranjan A, Tewari SK, Lehri A. Biological activities of Kalmegh (*Andrographis paniculata* Nees).
32. Okhuarobo A, Falodun JE, Erharuyi O, Imieje V, Falodun A, Langer P. Harnessing the medicinal properties of *Andrographis paniculata* for diseases and beyond: a review of its phytochemistry and pharmacology. Asian Pacific Journal of Tropical Disease. 2014;4(3):213-222.
33. Pandey AK, Mandal AK. Variation in morphological characteristics and andrographolide content in *Andrographis paniculata* (Burm. f.) Nees of Central India. Iranica J Energy Environ. 2010;1(2):165-169.
34. Pandey MK, Singh GN, Shrama RK, Lata S. Physicochemical standardization of *Andrographis paniculata* (Nees): an Ayurvedic drug. International Journal of Pharmaceutical research and development. 2011;3(6):81-89.
35. Patil R, Jain V. Andrographolide: A review of analytical methods. Journal of Chromatographic Science. 2021;59(2):191-203.
36. Paudel K, Ramamurthy A, Sharma G. Some important hepatoprotective medicinal plants in Ayurveda-a review. Int J Ayurveda Res. 2020;3(8):138-150.
37. Raina AP, Gupta V, Sivaraj N, Dutta M. *Andrographis paniculata* (Burm. f.) Wall. ex Nees (kalmegh), a traditional hepatoprotective drug from India. Genetic resources and crop evolution. 2013;60(3):1181-1189.
38. Raja RR, Pandiyan PS. *Andrographis paniculata* (Acanthaceae)-An Overview. Pharmacognosy reviews. 2016;1(2):283-298.
39. Rajani M, Shrivastava N, Ravishankara MN. A rapid method for isolation of andrographolide from *Andrographis paniculata* Nees (Kalmegh). Pharmaceutical Biology. 2000;38(3):204-209.
40. Richard EJ, Murugan S, Bethapudi B, Illuri R, Mundkinajeddu D, Velusami CC. Is *Andrographis paniculata* extract and andrographolide anaphylactic? Toxicology Reports. 2017;4:431-437.
41. Sabharwal S, Singh S, Anand N, Kaur S, Mehta M. An Overview on Kalamegha (*Andrographis paniculata*).
42. Sadhana HM, Joghee S. *Andrographis paniculata*–A Review. International Journal of Research in Pharmaceutical Sciences. 2020;11(4):5395-5400.
43. Sagadevan P, Suresh SN, Ranjithkumar R, Rathishkumar S, Sathish S, Chandarshekar B. Traditional use of *Andrographis paniculata*: review and perspectives. Int J Biosci Nanosci. 2015;2(5):123-131.
44. Sahu M, Rao SP. Review literature: *Andrographis paniculata*. Research Journal of Pharmacology and Pharmacodynamics. 2018;10(4):166-170.
45. Sanjutha S, Subramanian S, Rani CI, Maheswari J. Integrated nutrient management in *Andrographis paniculata*. Res J Agric Biol Sci. 2008;4(2):141-145.
46. Sareer O, Ahmad S, Umar S. *Andrographis paniculata*: a critical appraisal of extraction, isolation and quantification of andrographolide and other active constituents. Natural product research. 2014;28(23):2081-2101.
47. Sharma BK, Jain AK. Studies on some aspects of reproductive biology of *Andrographis paniculata* (Acanthaceae). Int J Plant Rep Biol; c2015, 7(2).

48. Sharma SN, Sinha RK, Sharma DK, Jha Z. Assessment of intra-specific variability at morphological, molecular and biochemical level of *Andrographis paniculata* (Kalmegh). Current Science. 2009:402-408.
49. Subramanian R, Asmawi Z, Sadikun A. A bitter plant with a sweet future? A comprehensive review of an oriental medicinal plant: *Andrographis paniculata*. Phytochemistry reviews. 2012;11(1):39-75.
50. Sule A, Ahmed QU, Samah OA, Omar MN. Screening for antibacterial activity of *Andrographis paniculata* used in Malaysian folkloric medicine: a possible alternative for the treatment of skin infections. Ethnobotanical leaflets; c2010, (4):8.
51. Tandon C, Mathur P, Sen M. *Andrographis paniculata* Nees (Kalmegh): A review on its antibacterial activities and phytocompounds. Eur J Med Plants. 2015;8(1):1-10.
52. Thakur AK, Chatterjee SS, Kumar V. Adaptogenic potential of andrographolide: An active principle of the king of bitters (*Andrographis paniculata*). J Tradit Complement Med. 2015;5(1):42-50.
53. Valdiani A, Kadir MA, Tan SG, Talei D, Abdullah MP, Nikzad S. Nain-e Havandi *Andrographis paniculata* present yesterday, absent today: a plenary review on underutilized herb of Iran's pharmaceutical plants. Mol Biol Rep. 2012;39(5):5409-5424.
54. Verma H, Negi MS, Mahapatra BS, Shukla A, Paul J. Evaluation of an emerging medicinal crop Kalmegh (*Andrographis paniculata* (Burm. F.) Wall. Ex. Nees] for commercial cultivation and pharmaceutical & industrial uses: A review. J Pharmacogn Phytochem. 2019;8(4):835-848.
55. Verma RK, Verma SK, Pankaj U, Gupta AK, Khan K, Shankar K. Improvement in the yield and quality of Kalmegh (*Andrographis paniculata* Nees) under the sustainable production system. Nat Prod Res. 2015;29(3):297-300.
56. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, *et al*. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020;10(5):766-788.
57. Ishihara T, Matsuda H, Takita Y. Doped LaGaO3 perovskite type oxide as a new oxide ionic conductor. Journal of the American chemical society. 1994 May;116(9):3801-3.
58. Reddy P. Pathophysiology of acute graft-versus-host disease. Hematological oncology. 2003 Dec;21(4):149-61.
59. Pramanick S, Banerjee S, Achari B, Das B, Sen AK, Mukhopadhyay S, *et al*. Andropanolide and isoandrographolide, minor diterpenoids from *Andrographis paniculata*: Structure and X-ray crystallographic analysis. Journal of natural products. 2006 Mar 24;69(3):403-5.
60. Wang Z, Gerstein M, Snyder M. RNA-Seq: A revolutionary tool for transcriptomics. Nature reviews genetics. 2009 Jan;10(1):57-63.
61. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]; c2001.
62. Sheeja K, Guruvayoorappan C, Kuttan G. Antiangiogenic activity of *Andrographis paniculata* extract and andrographolide. International immunopharmacology. 2007 Feb 1;7(2):211-21.