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REVIEW ON PHYTOPHARMACOLOGICAL ACTIVITIES OF *ANDROGRAPHIS PANICULATA* (BURM.F) NEES.

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ABSTRACT

Medicinal plants are in prevalence from the origin of the earth which has been efficiently used by ancient people as a cure for various ailments. The plant extracts are identified and act as an important source of active ingredient and secondary metabolite products such as alkaloid, terpenoids, which is used in curing diseases, for drug production and perpetuating good health by both the traditional and orthodox medical practitioners. The current aim of this review is to accumulate the morphological and pharmacological applications of *Andrographis paniculata* as a multipurpose drug showing efficient activity in curing various diseases. The plant is highly useful in curing various health ailments of human beings especially in viral diseases such as respiratory problems, HIV, Liver damage etc. The phytochemical tests revealed the presence of glycosides, saponins, tannins and alkaloids, but not of anthraquinones. Thus the plant has an important compound named as Andrographolide, a diterpenoid lactone having a diversity of pharmacological effects. The overdosage of the plant leads to some side effects like nausea, vomiting and loss of appetite Therefore, researchers have to perform various formulation for *A. paniculata* and develop a new drug molecules. The plant is to be widely cultivated and farmers should be encouraged in cultivating the medicinal plant which has multifarious therapeutic uses. The plant is considered as a safe, highly important medicinal plant for mankind.

KEY WORDS: ***Andrographis paniculata*, Biological Activities, Molecular characters, Elemental analysis, Anti HIV.**

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INTRODUCTION

Medicinal and aromatic plants are spread throughout the forest areas of South Asian places both in the tropical and subtropical belts. India has a rich diversity of plants having the medicinal values. Some plants are ubiquitously found in extreme environmental conditions, where plants grow very gradually and cannot live in any other environment. While some other plants are widely distributed and it can acclimatize more easily to various other ecological conditions. The primary metabolites such as proteins, phenols, sugars, starch and lipids which are useful in flavoring, fragrances, insecticides, sweeteners and natural dyes, are essentially required for the growth of plants.[1] The medicinal plants are also rich in secondary metabolites which have been used as a drug in pharmaceutical industry which includes alkaloids, glycosides, amines, insecticides, steroids, phenols, saponins, tannins, terpenoids, flavonoids etc.[2]The significant source for plants is the antioxidant activity which produces secondary metabolites. The antioxidant properties present in natural substances (food) for medicinal and preservative purposes[3]. An antioxidant terminates the chain reaction of a molecule that damages the cell by removing free radical intermediates present in it and then the oxidation reactions are inhibited by reducing the stress responsible for many degenerative disorders[4-5]. Natural products of higher plants may possess a new source of antimicrobial agents[6-7]. Thy infectious diseases are treated by the medicinal plants which mitigate many of the side effects which are associated with synthetic antimicrobials[8]. Cancer is a major dreadful disease caused by abnormal or uncontrolled cell division. About 6 million new occurrences of cancer are reported yearly worldwide. In the discovery of drug and its development; especially its activity against cancer and other infectious diseases[9] were natural products have played a significant role are prone mostly in low and middle income countries. The risk factors of cancer reported by WHO, noted that the use of tobacco, alcohol, low fruit and vegetable intake, and chronic infections are caused by hepatitis B virus (HBV), hepatitis C virus (HCV) and some types of human papilloma virus (HPV) are prevalent in the above mentioned countries[10].Mankind is most commonly affected by the widespread of vicious diseases like Malaria. The causative agent of the disease is caused by Plasmodium (Protozoa) of which four species *P. falciparam, P.vivax, P.ovale* and *P.malariae* are contagious to humans[11]. The disease is epidemic in tropical and sub-tropical areas of the world, especially because of the pitiless rise in the resistance of *P.falciparum* to commonly used antimalarial drugs like chloroquine, mefloquine, mepacrine, pyrimethamine, primaquine and sulphadoxin[12-13]. Viruses and bacteria present in the environment may cause upper respiratory infection. The occurrence of infection in nose, throat, sinuses, and ears is termed as upper respiratory infection. eg: common cold[14-15]. Three ingredients deoxyandrographolide, Andrographolide and neoandrographolide are effective in reducing inflammation[16]. Dermatophytosis is a fungal infection is one of the major health problems in tropical countries. The retroviridae family encompasses a group of viruses in which the replicative life cycle requires reverse transcription of the viral ribonucleic acid (RNA) genome into double stranded deoxyribonucleic acid (DNA). Retroviridae initially were identified in a variety of animal species in association with neoplasms such as leukemia and lymphoma; it subsequently was discovered that endogenous retroviral sequences are abundant in humans, comprising at least 1% of the human genome and demonstrating Mendelian inheritance patterns [17-19].The human immunodeficiency virus, or HIV, is the virus that causes HIV infection. The virus attacks and destroys the infection-fighting CD4 cells of the body's immune system. Loss of CD4 cells makes it difficult for the immune system to fight against the infections is transmitted (spread) through the blood, semen, genital fluids, or breast milk of a person infected with HIV. The main reason for the transmission of HIV to a healthy person is by unprotected sex or sharing drug injection equipment such as needles and syringes. A diagnosis of HIV is based on the first test that can be either an HIV antibody test (using blood, urine, or fluids from the mouth) or a plasma HIV RNA test (using blood). The second test always using blood is a different type of antibody test called a Western blot test. A positive Western blot test confirms that a person has HIV.*Andrographis paniculata* Nees belongs to the family of Acanthaceae commonly known as "Kalmegh" or "King of bitters". It is a perennial herb which is about 32 different species present in the genus *Andrographis*. Around 175 BC the plant *Andrographis paniculata* was recommended in *Charaka samhita* for the treatment of jaundice along with other plants in polyherbal preparations. In India, it is cultivated during rainy phase of summer season (kharif crop). The amount of organic matter present in the soil is best suitable for commercial cultivation of the crop.[20]In world, it is widely cultivated in China, Indonesia, Hong Kong, Philipines, the East and Mauritius [20-21] and West Indies such as Jamaica, Barbados, and Bahamas[115]Thailand, South Asia, South Africa, Java, Malaysia, Brunei, Singapore, India, Pakistan and Srilanka[110-111]. Cambodia, Caribbean islands, Laos, Myanmar, and Vietnam[112-113].This plant is also found in different phytogeographical and edaphic zones of China, America, West Indies, and Christmas Island[114]. In India, it is cultivated from Uttar Pradesh, Himachal Pradesh, Assam, Madhya Pradesh, Tamil Nadu, Karnataka and Kerala. In Tamil Nadu, it is cultivated in Tanjore, salem, Erode, Villupuram, Tiruchengode and Palayamkottai.

Taxonomical Classification

Kingdom	:	Plantae, Plants
Sub Kingdom	:	Tracheobionta, Vascular plants;
Super Division	:	Spermatophyta, Seed plants;
Division	:	Angiosperma
Class	:	Dicotyledonae
Sub class	:	Gamopetalae

Series	:	Bicarpellatae
Order	:	Personales
Tribe	:	Justicieae
Family	:	Acanthaceae
Genus	:	Andrographis
Species	:	*A. paniculata*(Burm. f) Nees[20]

***Vernacular names*[116 -117]**

Arabic	:	Quasabhuva
Assamese	:	Chiorta, Kalmegh
Azerbaijani	:	Acılar Şahı, Acılar Xanı (khanı)
Bengali	:	Kalmegh
Burmese	:	Se-ga-gyi
Chinese	:	Chuan Xin Lian
English	:	The Creat, King of Bitters
French	:	Chirette verte, Roi des amers
Gujarati	:	Kariyatu
Hindi	:	Kirayat, Kalpanath,
Indonesian	:	Sambiroto, Sambiloto
Japanese	:	Senshinren
Kannada	:	Nelaberu
Konkani	:	Vhadlem Kiratyem
Lao	:	La-Sa-Bee
Malay	:	Hempedu Bumi, Sambiloto
Malayalam	:	Nelavepu, Kiriyattu
Manipuri	:	Vubati
Marathi	:	Oli-kiryata, Kalpa
Mizo	:	Hnakhapui
Oriya	:	Bhuinimba
Panjabi	:	Chooraita
Persian	:	Nain-e Havandi
Philippines	:	Aluy, Lekha and Sinta
Russian	:	Andrografis
Sanskrit	:	Kalmegha, Bhunimba and Yavatikta
Scandinavian	:	Green Chiratta
Sinhalese	:	Hīn Kohomba or Heen Kohomba
Spanish	:	Andrografis
Tamil	:	Nilavembu
Telugu	:	Nilavembu
Thai	:	Fa-Talai-Jorn, Fah-talai-jon (jone)
Turkish	:	Acılar Kralı, Acı Paşa, Acı Bey
Urdu	:	Kalmegh, Kariyat, Mahatita
Vietnamese	:	Xuyên Tâm Liên

MORPHOLOGICAL CHARACTERS OF A. PANICULATA118-119

The leaves and roots of *A. paniculata* have been traditionally used in Asia and Europe over the periods for different medicinal purposes as a folktale remedy for a wide spectrum of ailments[61.] The plant generally grows up to a height of 30-110 cm in moist shady places. The morphological appearances of leaves are simple, dark in color, opposite, lanceolate, glaborous, 2- 12cm long, 1-3cm wide, acute apex, and entire margin[22]. The stem is acutely quadrangular or Tetrangular in outline; can be broken easily due to its fragile texture and it is much branched. Roots showed the presence of secondary growth which is visible. Inflorescence of the plant is 10-30 mm long; bract small; pedicel short.[20,24-27] Flower consists of small, linear 5 particle, calyx; tube narrows, about 6mm long white corolla with violet markings. Two stamens inserted in the throat and two celled superior ovary.1-2cm long, 2-5mm wide, linear-oblong, compressed, erected capsule[28]. Seeds are numerous, sub quadrate and yellowish brown. Micropropagation is the proven method for efficient *in vitro* propagation of medicinal and aromatic plants and for commercial exploitation of valuable plant-derived pharmaceuticals[29-35].

MORPHOLOGY OF ANDROGRAPHIS PANICULATA

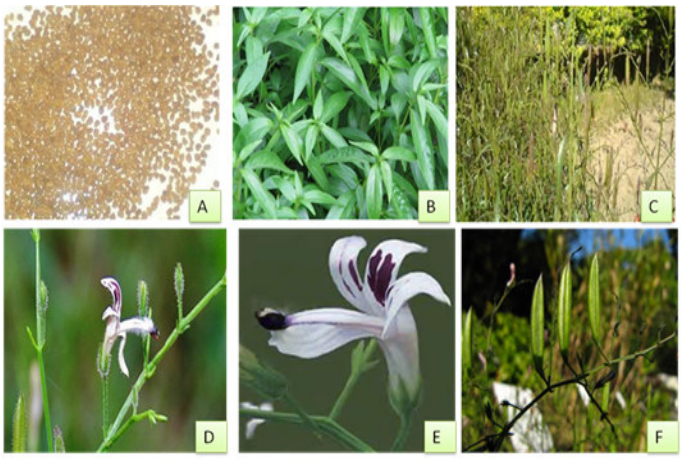


Figure 1
A) Mature seeds B) Leaves C) Aerial parts with mature and immature capsule; D) Flower buds E) Entire flower F) Mature Fruit (Photo courtesy: Ankita kataky, 2010).

Table 1
Morphological characters of Andrographis paniculata.

1	Plant height	30–110 cm
2	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
3	Leaves	Glabrous
	Length	2–12 cm
	Width	1–3 cm
	Arrangement	Lanceolate
	Shape	Pinnate, acute apex, entire margin
4	Flowers	White with rose-purple spots on the petals
	Size	Small, in lax spreading axillary and terminal racemes or panicles
5	Seed	Capsules linear-oblong, acute at both ends
	Size	1.9 cm × 0.3 cm
	Color	Yellowish brown
	Shape	Subquadrate, numerous
6	Flowering and fruiting	December to April

MICROSCOPICAL STRUCTURE OF A. PANICULATA

Angles of *A. paniculata* stem are short with winged projections which consists of single layer epidermial cell and a group of parenchymatous cells; having the ridges in between which are shallow; compactly arranged cells with a thin cuticle and it is allied with glandular hairs externally; 2-5 cell layer thick walled hypodermis, cells more or less rounded or polygonal, thin, compactly arranged with the presence of chlorophylls; cortical cells are 5 to 6 layer thick, rounded, thin walled, compact, and parenchymatous; stele amphipholic siphonostele subjugating supreme part of the stem, spreaded more to the ridge area a few sclerenchymatous cell in the periphery of vascular bundles groups comprises of 2 to 4 or even solitary throughout; external phloem is thin layered whereas internal phloem occurs mostly in patches; xylem disturbed with medullary rays; pith parenchymatous, cells polygonal to rounded, larger in size, thick walled, and compactly arranged without any content[23].Roots of epiblema is replaced by cork layer, three different separate zones of which cells of peripheral layer are arranged loosely, inner cells are smaller but arranged compactly; stele occupies the maximum part of the root being the secondary growth; xylem and ray cells are distinct in rows, primary vascular bundle crushed; pith insignificant having few parenchymatous smaller cells[23].The leaves of *A. Paniculata* showed the presence of diacytic stomata at lower epidermis, trichomes may be glandular or non-glandular, large cystoliths, columnar palisade cells, beneath epidermal layer, collenchymas are present in midrib; spongy parenchyma cells; vascular bundles are spiral, scalariform and reticulate lignified xylem vessels in the upper part and lignified phloem in the lower part with small acicular calcium oxalate crystals, a film of lower epidermal cells showed wavy-wall, dense collenchyma at the corners of stems, a layer of thick-walled endodermis and parenchyma cells incorporates chloroplastid.[28]

MICROSCOPICAL SECTION OF A. PANICULATA

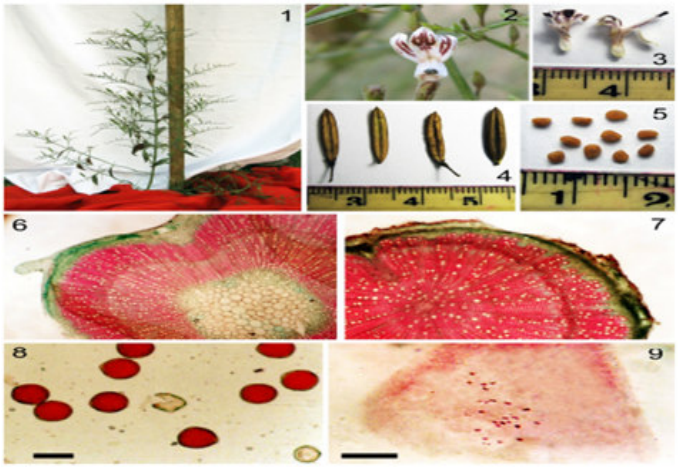


Figure 2

1- Matured erect branched plant; 2- Flower lobes showing pigmentation; 3- Dark purple anther; 4- Fruits; 5- Golden brown seeds; 6- T.S. of stem; 7- T.S. of root; 8-Stained and unstained pollen grains; 9- Metaphase I (Datta Kumar, 2012).

NURSERY

For the cultivation of *A. paniculata* in a small scale nursery, vermicompost coir pith are used for the recovery of soils from industrial sites[36]. Seeds were collected and sown in polythene bags. The nursery beds were prepared for three treatments with biocompost, vermicompost, farmyard manure and one bed for control. The treatments were added to soil in 1:2 ratios. After few days of seed germination plantlets were transplanted in respective beds. After every two months three samples were taken from each bed. The plantlets were uprooted. Increased shoot length was observed in vermicompost treatment (10.11cm) followed by farmyard manure, biocompost and control. The increase in growth may have been due to increases in microbial biomass in soils receiving vermicomposts which increased nutrient mineralization[142].

SOIL CONDITIONS

It is cultivated in soil types, particularly serpentine soils which are legitimately high in metals such as copper, zinc and aluminium and no other plant can be cultivated in such soils[37]. Wet soil or flooded soil is side stepped for its cultivation[38].

HARVESTING PERIODS

A. paniculata is upraised from seeds and favors sunny condition. The seedlings elevated in nursery beds should be transplanted to field at a distance of 60 cm × 30 cm with three irrigations during that period, predominantly at flowering stage. In India, the seeds are sown in the months of May – June, flowers during August – November and the whole plant starts maturing during February – March. Maximum harvest of total diterpene lactones was noted as flourishing from the aerial part[39-41]. The best harvesting period of *A. paniculata* leaves is at 3-5 months old or at 50% blossom where the highest quantity of active lactone compounds were present followed by final harvesting after next 2-3 months, with an yield of 3 ton per hectare (fresh weight) or 0.5-1 tons per hectare (dried weight)[42].

PROPAGATION

After 6 weeks of sowing, the seedlings were transplanted in the main field at the spacing of 15 x 15 cm. The crop were uniformly applied with 75 kg each of Nitrogen, Phosphorous and 50 kg of Potassium per hectare and cultural operations like irrigation, weeding were practiced. The propagation of *A. paniculata* generally occurs through the seeds. In the natural habitat, it is found growing in clay to sandy loamy soil rich in organic matter is good for its growth and yield[137]. After the application of FYM positively influenced seedling growth of kalmegh in the nursery. At transplanting age (47 DAS) highest seedling height with maximum number of leaves was obtained with 14 kg/m^2 FYM application[48].

GENETIC MALE STERILITY

Genetic male sterility induced (6.0 to 14.0%) in *A. paniculata* at M_1 following 20 kR gamma irradiation was reported by Lattoo *et al.,*(2006) [43]monogenic recessive to normal was found in the male sterile gene. It acted upon the tapetal layer and also affects the non sporogenous tissue within the anther locule resulting in infringement of the locule and thereby, significantly it reduces the production of pollens and enhances the creation of abortive pollen. However, female fertility in *A. paniculata* remained unimpaired and completely intact.

TISSUE CULTURE TECHNIQUES

The regeneration of shoot buds from organogenic calli was varied on the basis of the culture medium composition. About 75.3% in case of leaf-derived calli and 63.4% in case of stem-derived cultures showed

shoot bud regeneration in the medium having 3.0 mg/L BA, 50 mg/L Ads and 1.0 mg/L NAA after six weeks of first subculture. The increase of NAA concentration higher than 2.0 mg/L suppressed the rate of shoot bud regeneration and slow growth of the organogenic calli. The maximum number of shoot buds (28.6) was obtained in the medium containing 3.0 mg/L BA, 50 mg/L Ads and 1.0 mg/L NAA after four weeks of culture initiation. A high frequency of shoot production from organogenic calli could be obtained by manipulating the growth regulators and culture condition. There were differences between treatments both in the percentage of cultures with response and in the mean number of shoot buds per culture.Effect of BAP (1.0 µM) in combination with other cytokinins (0.5-10.0 µM Kn, 2iP and TDZ) were tested and results showed synergetic effect of cytokinins and induced number axillary shoots. The results were best at BAP (1.0 µM) in combination with Kn (5.0 µM) and 39.08 shoots developed after six weeks of culture. However, combination of BAP + 2iP and BAP + TDZ was not much beneficial in triggering the percentage of responding explants and provoking multiple shoot formation indicating that multiple shoot formation depends on the optimum balance of growth regulator combination and concentration in the medium. Similar differential response was observed[139].

INDUCTION OF ROOTING AND ACCLIMATIZATION

Elongated shoots were excised and placed in half or full strength MS medium supplemented with various concentrations of IBA or NAA for root induction. Full strength MS medium without growth regulators did not promote root induction; roots were observed in media containing ½ strength MS medium supplemented with NAA or IBA with 2% sucrose. However, optimal rooting and growth of micro shoots were observed in medium containing 0.5 mg/L IBA or NAA with 2% sucrose after 9 to 11 days of culture without intervening callus. The maximum percentage of rooting (76.2%) was obtained in the medium containing 0.5 mg/L IBA within three weeks of culture. Root development was however, slow at higher concentrations of IBA or NAA. The rooted plantlets were transferred into pots for acclimatization. About 60% of the rooted plantlets survived in the pot one week after the transfer and then the plants were grown normally. A successful production of shoot bud regeneration from leaf and stem explants and induction of roots from excised root were dependent on the nutrient medium and the culture conditions.

TISSUE CULTURE OF A. PANICULATA.

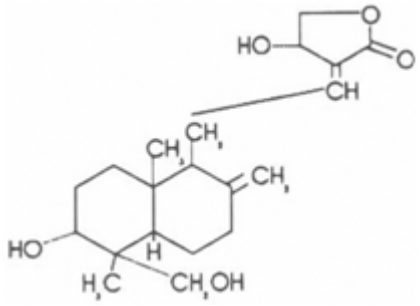
Figure 3

A) Organogenic calli development from leaf explant on medium having 3.0 mg/L BAP + 50 mg/L Ads + 1.0 mg/L NAA after 6 weeks of initial culture. B) Shoot bud regeneration (arrows) from Organogenic calli on medium having 3.0 mg/L BAP + 50 mg/L Ads + 1.0 mg/L NAA after 6 weeks of subculture. C) Root initiation from micro shoots of Andrographis paniculata after 3 weeks of culture of ½ strength MS medium supplemented with 0.5 mg/L IBA + 2% sucrose. D) Plantlets established in the pot. (Picture courtesy - Bansi and Rout (2013)).**Compounds in *A. paniculata***

The plant extract is known to contain diterpenes, flavonoids and stigmasterols. Flavonoids are present more in roots and leaves. From the soluble fractions of the ethanol or methanol extract, 5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-7,8,2',5'-tetramethoxyflavone, 5-hydroxy-7,8,2',3'-tetramethoxyflavone, 5-hydroxy-7,8,2'-trimethoxyflavone, 7-*O*-methylwogonin and 2'-methyl ether were isolated as the main flavonoids. "The aerial parts contain alkanes, ketones, and aldehydes. Andrographolide is the key constituent having a molecular formula as $C_{20}H_{30}O_5$, and is believed to be the active constituent for biological activities and represents as an identity indicator for the plant. Melting point of Andrographolide is 230°-239°C. (3 - (2 – decahydro - 6 – hydroxyl – 5 - (hydroxymethyl) – 5, 8a - dimethyl – 2-methylenenaphthyl) ethylidene) dihydro-4-hydroxyfuran- 2 (3H) – one) is the reported IUPAC name of andrographolide. The compound Andrographolide can be easily dissolved in methanol,

ethanol, pyridine, acetic acid and acetone, but slightly dissolved in ether and water. Growing region and seasonal changes have a strong impact on formation of the diterpene lactones. The highest concentration of the active components is found just before the plant blooms, making early fall the best time to harvest[44&20].

Molecular structure of Andrographolide



The other important compounds isolated from different parts of *A. paniculata* are apigenin-7, 40-di-omethyl ether, carvacrol, eugenol, myristic acid, hentriacontane, tritriacontane, or oxylon A and wogonin[45]. the chemical composition of *Andrographis paniculata* showed that it is a rich source of deterpenoids and 2'-oxygenated flavonoids including andrographolide, neoandrographolide, 14-deoxy-11,12-didehydroandrographolide, 14-deoxyandrographolide, isoandrographolide and 14-deoxyandrographolide 19 β-D-glucoside, homoandrograholide, andrographan, andrographosterin, stigmasterol[46&48;21] andrographiside, deoxyandrographiside, homoandrographolide, andrographan, andrographon, andrographosterin[20].

BIOACTIVITIES OF A. PANICULATA

The plant is used as bitter stimulant, antispasmodic, antiperistaltic, stomachic and also an antihelmintic. It has been active with various advantages in case of general weakness in recuperation after fevers, disorders of liver and advanced stages of dysentery[49]. The plant is also cast off to treat gastro-intestinal tract and upper respiratory infections, fever, herpes, sore throat, and a variety of other chronic and infectious diseases. The fresh leaves of *A. paniculata* juice of are a domestic remedy in the treatment of colic pain, loss of appetite, irregular stools and diarrhea [50& 20]

BIOACTIVITIES OF ANDROGRAPHOLIDE

The bioactivities of some of the andrographolide compounds are as follows;14-deoxyandrographolide responsible for activation of NOS and guanylate cyclase vasorelaxation *in vitro* and *in vivo* [51-53]; neoandrographolide - NO, PGE2, iNOS and COX-2 in activated macrophages CCl4, tBHP-induced hepatotoxicity (*i.p* 100 mg/kg, 3d)[54-56]; 14-deoxy-11,12 didehydroandrographolide - muscle relexation and Nitric oxide release from endothelial cells[57-58]; 14-deoxy-14,15-didehydroandrographolide - cytotoxic activity and cell cycle arrest of tumor cells NF-κB-dependent trans-activation[59-60]; andrograpanin - protein kinase or p38 MAPKs pathways chemokine SDF-1α induced chemotaxis in Jurkat and THP-1 cells[61-62]; isoandrographolide - cell-differentiation-inducing activity proliferation of HL-60 cells[63-64]; 14-acetylandrographolide - growth of leukemia, ovarian, renal cancer cells[65] 19-*O*-acetyl anhydroandrographolide - NF-κB-dependent trans-activation[60].

PHARMACOLOGICAL EFFECTS

Some of the pharmacological effects of andrographis are followed as, Abortifacient which can abort pregnancy. Acrid which is rubifacient to the skin; Analgesic; Antibacterial; Antidiarrhoeal and intestinal effects; Anti-inflammatory activity; Antimalarial activity; Antioxidant activity; Antipyretic; Anti snake venom; Antithrombotic; Antiviral; Cancerolytic; Cardiovascular activity; Choleretic; Depurative; Expectorant; Hypoglycemic activity; Hepatoprotective activity; Immunological potential; Laxative; Psychopharmacological activity; Sedative; Thrombolytic; Vermicidal.[20-21]

ANTIOXIDANT EFFECTS

Verma and Vinayak (2008)[143] related the antioxidant effects of the aqueous extract on liver defense systems in lymphoma bearing mice. The aqueous extract and hydro alcoholic extract of the medicinal plant *A. paniculata* showed the increase in activities such as catalase, superoxide dismutase and glutathione-S-transferase enzymes and reduced lactate dehydrogenase activity. The results performed with that of aqueous extract of *A. paniculata* exhibited a greater antioxidant activity than the ethanol extract in all model systems tested. The function of Hydroalcoholic extract of *A. paniculata* possesses oxidative alterations in myocardium and confers substantial cardioprotective activity by facilitating in retaining the cardiac function in a norma manner[66].

ANTI-DIABETIC ACTIVITY

Radhika and her coworkers (2012)[144] using carrageenan induced rat hind paw oedema modelfor acute inflammation. The anti-inflammatory activity of chloroform extract of *Andrographis paniculata* stem was determined by Ibuprofen as a standard drug. In 6th hour

at a dose of 200mg/kg the chloroform extract of *Andrographis paniculata* stem showed good effect and was comparable with the standard drug Ibuprofen (10 mg/kg) ($t = 64.06$, $p< 0.001$)[67]. The compound Andrographolide reduces the plasma glucose concentration in streptozotocin induced in both the diabetic rats and in normal rats, having a significant effect in normal rats than on diabetic rats and in addition to it an intravenous glucose is retort to the normal rats and enhances the uptake of radioactive glucose by isolated soleus muscle of streptozotocin-diabetic rats in a concentration-dependent manner. Intravenous administration of andrographolide in diabetic rats for continuous three days indicates that the glucose lowering effect of andrographolide is due to better utilization of glucose by skeletal muscle which results in increase in mRNA and protein levels of glucose transporter (GLUT4) in the soleus muscle.[68]However, after in vitro experiments, Wibudi and his coworkers[145] (2008) determined that the hypoglycemic effect of *Andrographis paniculata* is due to insulin released from pancreatic β-cells through ATP-sensitive potassium channels, similar to other insulinotropic antidiabetic agents[69].

ANTIDIARROHEAL ACTIVITY

The inflammation can be caused by pathogenic bacteria growth or a viral or parasitic infections and irritations. Medications and certain foods are the sources of pathogenic growth. *Campylobacter, Salmonella, Shigella* and *Escherichia coli* are common bacteria that cause diarrhoea. Although antibiotics are effective in treating bacterial infections, antibiotic-resistant strains of bacteria can be produced by the overuse of antibiotics. Many drugs, such as kaolin-pectin, loperamide and bismuth are used to relieve the symptoms of diarrhoea, but they may cause undesirable side effects[70]. The *A. paniculata* components, Andrographolide and neoandrographolide showed comparable activity to loperamide (Imodium), the most common anti-diarrhoea drug. In Thailand, a methanolic extract was made to boil *A. paniculata* stem was testified to be effective against *Proteus vulgaris* and combined powder of stem and leaves can be effective against the *Shigella* bacteria [71]. In an experiment conducted in a pharmacological research institute in Shanghai, China, 165 patients were given tablets of *A.paniculata* which is equal to the amount of 15.6g crude powder per day. Fluroxone, a common drug used to treat dysentery were given to 28 patients. The result significantly showed the effective rate of *A. paniculata* was 75.2% than that of Fluroxone was 71.4%[72]. *A. paniculata* was believed to be effective against bacterial dysentery and diarrhea because it has antibacterial activities. In a study conducted on mice, it was found that 50% and 85% alcohol extracts of *Andrographis paniculata* leaf powder were effective in reducing intestinal tract movements[73].

ANTIMICROBIAL ACTIVITY

The plant *Andrographis paniculata*, is an antibacterial agent capable of responding the ill effects caused by pathogenic microbes[74-77]. The antimicrobial activity of aqueous leaf extract of *A. paniculata* was found to have antibacterial activity against *Bacillus subtilis* and *Streptococcus aureus* by Manjusha *et al* (2011)[79]. A similar conclusion was reported by Radha *et al* (2011)[94] who found that petroleum ether, acetone, chloroform and methanol extracts of *A. paniculata* leaves and stems, showed significant antimicrobial potential against *Enterococcus faecalis*, *Streptococcus pyogenes, Klebsiella pneumonia* and *Proteus vulgaris*. The ethanolic leaf extract and andrographolide compound isolated from the leaves are potent in inhibiting these bacteria and the work highlights that the inhibitory effect with standard antibiotics.*In vitro* screening of the aqueous extract of *A. paniculata* posses' potential antibacterial activity towards both gram-positive and gram-negative microorganisms where the methanolic extracts inhibited the growth of 95% organisms tested, followed by chloroform extracts inhibited 80%. Hexane extracts inhibited 65% growth of the tested organisms[80]. The antimicrobial activity of aqueous extract of *Andrographis paniculata* or andrographolides and arabinogalactan proteins from *A. paniculata* when evaluated, showed significant antimicrobial activity, which may be due to the combined effect of the isolated arabinogalactan proteins and andrographolides[81].

ANTICANCER ACTIVITY

Chen and his coworkers (1982)[48] reported that a major mediator of the inflammatory response is elevated interleukin-6 (IL-6), has been concerned in androgen receptor (AR) activation, cellular growth and differentiation, which plays an important role in the development and progression of prostate cancer, and is a potential target in cancer therapy. Through screening of drug using human prostate cancer cell lines expressing that IL-6 autocrine loop, showed the presence of andrographolide, a diterpenoid lactone isolated from a traditional medicinal plant. *Andrographis paniculata*, could significantly inhibit and suppresses the IL-6 expression and its mediated signals. Andrographolide inhibits IL-6 expression at both mRNA and protein levels in a dose-dependent manner and it suppresses both IL-6 autocrine loop and paracrine loop induced cell signaling including Stat 3 and Erk phosphorylation. Furthermore, andrographolide hinders cell viability and induces apotopsis in both androgen stimulated and castration resistant human prostate cancer cells deprived of causing substantial toxicity to normal immortalized prostate epithelial cells. Moreover, treatment of andrographolide to mice bearing castration-resistant DU145 human prostate tumors that express constitutive IL-6 autocrine loop significantly suppresses tumor growth. These results demonstrate that andrographolide could be developed as a therapeutic agent to treat both androgen stimulated and castration resistant prostate cancer possibly by suppressing IL-6 expression and IL-6 induced signaling[82].Andrographolide is the key compound used in the treatment which inhibited the in vitro proliferation of different tumor cell lines, signifying numerous types of cancers. The compound exerts direct anticancer activity by cell-cycle arrest at G0/G1 phase through induction of cell-cycle inhibitory protein p27 and decreased expression of cyclin-dependent kinase 4 (CDK4).

Immunostimulatory activity of andrographolide is demonstrated by increased proliferation of lymphocytes and production of interleukin-2. Andrographolide also enhanced the tumor necrosis factor-α production and CD marker expression, resulting in increased cytotoxic activity of lymphocytes against cancer cells, which may contribute for its indirect anticancer activity. The *In vivo* anticancer activity of the compound is further substantiated against B16F0 melanoma syngenic and HT-29 xenograft models and the results suggest that andrographolide is an interesting pharmacophore with anticancer and immunomodulatory activities and hence has the potential for being developed as a cancer therapeutic agent.

ANTI-PLASMODIAL ACTIVITY

In vitro studies of Dua and his coworkers (2004)[146] revealed that compound 1,2-dihydroxy- 6,8-dimethoxy-xanthone possessed substantial anti-plasmodial activity against *Plasmodium falciparum* with its IC_{50} value of 4 μg ml^{-1}. Xanthones bearing hydroxyl group at 2 positions demonstrated most potent activity while xanthones with hydroxyl group at 1, 4 or 8 position possessed very low activity. *In vivo* antimalarial sensitivity test of this compound on Swiss Albino mice with *Plasmodium berghei* infection using Peters' 4-day test gave substantial reduction (62%) in parasitaemia after treating the mice with 30 mg kg−1 dose[84] The methanolic extract significantly inhibited *Plasmodium falciparum* at a 50-percent inhibitory concentration (IC50) of 7.2μg/mL[85].

ANTICOLD ACTIVITY

One clinical trial has investigated the efficacy of a standardized *A. paniculata* extract to prevent the common cold by Caceres 107 healthy students in a rural school had daily taken either placebo or a dose of 200 mg (minimum 5.8%) of Kan Jang (a formulation of *A. paniculata* provided by the Swedish Herbal Institute) for three months. The number of colds occurring over a three month period was observed. After 1 month no significant difference was found. However, the difference was statistically significant in the second and third month. The placebo group was 2.1 times more likely to catcha cold than the Kan Jang group. The incidence of the common cold was 30% in the *A. paniculata* group, whereas the incidence was 62% in the placebo group[86].

DYSENTERY OR GASTROENTERITIS

Akbar (2011)[110] reported that the Ethanol extract tablets of *A. paniculata* were reported to cure 88.3 percent of acute bacillary dysentery and 91.3 percent of acute gastroenteritis cases. Andrographolide administration was reported to cure 91 percent of acute bacillary dysentery cases.[140]

ANTI-INFLAMMATORY EFFECT

Deng *et al* (1982)[147] also suggested *A. paniculata* might exert through stimulation of the adrenal gland since the herb showed no effect when the adrenal gland of the animals were totally removed[87]. Hidalgo *et al* (2005)[89] suggested its anti-inflammatory effect involved Andrographolide inhibiting a nuclear factor kappa B (NF-kappaB) binding to DNA in endothelial cells or HL-60-derived neutrophilic cells, and thus decreasing the expression of proinflammatory proteins [88&89]. In a study from Thailand, rats were given injections with carrageenan (an agent for stimulating inflammation) to study the anti-inflammatory effect of *A. paniculata* extract ranging from 500-1250, 2500 mg/body weight. The result showed that aqueous extract of *A.paniculata* effectively reduced the paw volume in rats treated with *A.paniculata* whereas the control group did not [90].Amroyan *et al* (1999)[91]found that Andrographolide from *Andrographis paniculata* did not affect the biosythesis of eicosanoids, but inhibited the platelet-activating factor (PAF) induced human blood platelet aggregation where eicosanoids and PAF are two of the most important inflammatory mediators. Inhibition of the biosythesis of eicosanoids is characteristic for non steroidal anti-inflammatory drugs, while PAF antagonists are used as potential agents in inflammation. This mechanism is most likely combined with the cardiovascular and antithrombic activity of A. paniculata [91].

ANTIVIRAL ACTIVITY

Andrographolide, neoandrographolide and 14-deoxy-11,12- didehydroandrographolide are reported to be viricidal against herpes simplex virus 1 (HSV-1) without having any significant cytotoxicity at viricidal concentrations[93].

ANTI- HIV ACTIVITY

Stephen and Comac (2000)[148] indicated that extracts of *Andrographis paniculata* may have the potential for interfering with the viability of the Human Immuno Deficiency Virus (HIV) and advised that *A. paniculata* could combine with modern medicines against Acquired Immuno Deficiency Syndrome (AIDS) A phase I dose-escalating clinical trial conducted in 13 HIV patients showed a significant rise in the mean CD4(+) lymphocyte level but with no significant changes in mean plasma HIV-1 RNA levels of HIV- 1 infected patients after administration of the regimen. The findings proved that andrographolide may inhibit HIV-induced cell cycle dysregulation leading to a rise in CD4 (+) lymphocyte levels in HIV-1 infected individuals[92].

ANTI-FUNGAL ACTIVITY

Radha *et al* (2011)[94] examined the petroleum ether, acetone, chloroform and methanolic extracts of *Andrographis paniculata* leaves and stems, in order to evaluate the antifungal potential of *Candida albicans* and *Aspergillus flavus*. The yeast, *Candida albicans*

showed susceptibility to 75% of chloroform extracts of the leaves (23.33; 1.20mm) and the acetone extracts of stems showed inhibitory effect on the growth of the fungus, *Aspergillus flavus* (23.67; 0.88mm)[79.] Similar studies were conducted by Bobbarala *et al* (2009)[80]. against *Acremonium strictum, Alternaria alternata, Aspergillus flavus, Bipolaris bicolor, Cladosporium herbarum, Curvularia lunata, Fusarium oxysporum, Penicillium expansum, Rhizoctonia solani, Tiarosporella phaseolina* and *Ustilago maydis* using hexane, chloroform and methanolic extracts and the results revealed that the methanolic extract showed activity against *Alternaria alternate* whereas, the chloroform extracts showed greater activity against *Fusarium oxysporum*[95].

OTHER ACTIVITIES

Xanthones isolated from the roots showed antiprotozoal activity against *Trypanosoma brucei, Trypanosoma cruzi* and *Leishmania infantum*[96]. The compound 1,2-dihydroxy-6,8-dimethoxy-xanthone possessed substantial antiplasmodial activity against *Plasmodium falciparum* with its IC_{50} value of 4 μgml^{-1}. Xanthones bearing hydroxyl group at 2 position demonstrated most potent activity while xanthones with hydroxyl group at 1,4 or 8 position possessed very low activity[84]. Nematicidal efficiency of water and methanolic extracts of *Andrographis paniculata* were evaluated *In vitro* against root knot nematode, *Meloidogyne javanica* and reniform nematode, *Rotylenchulus reniformis* by Goel *et al (*2009).[96] Crude fractions of aerial parts of *Andrographis paniculata* were evaluated for growth-inhibitory and oviposition-deterrent activity against larval and adult stages of Bihar hairy caterpillar, *Spilarctia oblique* (Arctiidae). The methanol fraction had the highest growth inhibitory activity. The diterpene andrographolide, displayed significant growth-inhibitory antifeedant properties with GI_{50} and FD_{50} values of 100.4 and 159.7 µg/g diet respectively. The ethyl acetate fraction possessed the highest oviposition-deterrent activity[98].*Andrographis paniculata* including andrographolide, a major diterpenoid component and its analogues have been reported to exhibit a marked effect on hepatic bio-transformation enzymes, i.e., aniline hydroxylase, *N*- and *O*-demethylase[99]alanine aminotransferase and aspartate aminotransferase[100]including phase II enzymes, i.e., glutathione *S* transferase and DT-diaphorase[101]. Modulatory influence of *Andrographis paniculata* extract on a responsive isoform of hepatic CYPs was recently reported in mouse hepatic microsomes compared to typical CYP-inducers (3-MC for CYP1A and PB for CYP2B), in terms of total CYP content and related alkoxyresorufin *O*-dealkylase activities[102]

HYPOTENSIVE ACTIVITY

Andrographis paniculata, is reported to have, by acting through β- adrenoceptors, autonomic ganglion receptor andangiotensin converting enzyme (ACE) inhibitory activity[103]. The 4th week of the extract treatment in SH rats significantly increases the relaxation responses to ACh as a result of possible improvement in the endothelial function, these are comparable with the study. Conversely the plant possesses a remarkable capability to challenge the nor-epinephrine induced contractions resulting in vasorelaxation in isolated rat[104]. The improvement in relaxation responses to ACh following chronic administration of chloroform extract is most likely due to the activation of NO synthase and ultimate stimulation of NO production in endothelial cells. Moreover, the effects of chronic administration are evidently suggestive of increased responsiveness of the vascular smooth muscle to NO since 4-week treatment with the extract was found to enhance the relaxation responses to the action of the endothelium-independent vasodilator SNP. Endothelial protective effects of *Andrographis paniculata* chloroform extract were comparable to the effects of Verapamil, which acts by blocking the L-type Ca2+ current and high K+ activated pathways to relax the smooth muscle[105].

ANTIVENOM ACTIVITY

Plant extracts (7.2 mg/kgbody weight) and partially purified fractions (2.4mg/kgbody weight) when orally administered to mice experimentally envenomed with rattle snake venom injection (2.5- 15 mg/kg body weight) showed potent neutralizing effect against the venom. The isolated fractions effectively inhibited the toxic effect of snake venoms *in vitro* than *in vivo.*[138]

BIOFILMS

The antibiofilm activity of the extract on the exopolysaccharide (EPS) was determined using a modified gradient plate technique with Congo red medium *P. aeruginosa* isolates were grown in plant extract incorporated trypticase soy broth for 18 hours and allowed to form a biofilm. Water and tobramycin were the negative and positive controls, respectively. After incubation at 37°C, they were stained with crystal violet (0.1%) and quantified using microtitre analysis (OD 490 nm). A continuous gradient of plant extract on CRA medium was prepared, and the biofilm forming isolates were inoculated into the centre of the plate as a single streak. The organisms were again streaked zigzag perpendicular to the original streak crossing it each time. The colour and nature of the developed colonies along the streaked line were observed[106]. The crystal structure of *P. aeruginosa* 3JPU (*P. aeruginosa* LasR, transcriptional regulator of Las QS system), 2B4Q (RhlG, beta-ketoacyl reductase, QS regulated virulence factor rhamnolipid synthesis enzyme) and 2W38 (*P. aeruginosa* sialidase, *in vivo* biofilm formation enzyme) were retrieved from the NCBI-PubChem database. Protein–compound docking simulation was performed using AutoDock 4.0[108]. The ADME molecular properties and bioactivity scores of the drug targets were calculated using Molinspiration according to Lipinski's rule for all analysed ligands[109].

MACROMUTANT ACTIVITY

Ghosh *et al* (2012).[23] screened 14 viable (*S. viridis*, *lax branching*, *bushy*, *unbranched I* and *II*, *dark green leaf*, *broad leaf I* and *II*, *narrow leaf I* and *II*, *drooping leaf I*

and *II*, *dwarf* and *early maturity*) at M_2 following EMS and dES treatments. Mutation frequency over M_2 population was 2.82% and *lax branching* mutant was maximum (0.51%). EMS induced relatively higher (3.12%) frequency of mutation than dES (2.46%). The mutant traits were monogenic recessive mostly (*S. viridis* showed digenic mode of inheritance). All mutants bred true in M_4 generation. Meiotic analysis revealed 2n=50 chromosome in mutants alike to control. Andrographolide (estimated from matured leaves by HPTLC) content (control: 3.41%, mutants: 0.03 to 3.99%) was significantly higher in *bushy* and *broad leaf I* and *II* than normal plants. The mutants induced were considered to be important genetic resources in the plant species.

MOLECULAR WORKS OF ANDROGRAPHIS PANICULATA

In plants, plastidial 2C-methyl-D-erythritol-4-phosphate (MEP) and cytosolic mevalonic acid (MEV) pathways provide two 5C isoprenoid building blocks, dimethyl allyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP), for the biosynthesis of diverse terpene metabolites[120]. IPP and DMAPP derived from the MEP pathway are converted to monoterpenes, diterpenes, and tetraterpenes, whereas those derived from the MEV pathway are converted to sesquiterpenes and triterpenes. However, cross-talk between these two pathways in biosynthesis of some terpenes was also recognised [121- 123]. Previously, a major role of the MEP pathway and a minor role of the MEV pathway for supplying the 5C isoprenoid precursors for the biosynthesis of andrographolide were reported[124]. Transcripts predicted to encode all the enzymes of the MEP and MEV pathways are identified in kalmegh transcriptome which demonstrates the quality and in-depth coverage of the transcriptome database. Interestingly, four transcripts for DXS, three for DXR and two each for HDS, HDR, AACT, HMGS, HMGR, PMK, MVD and IDI were revealed in kalmegh transcriptome. This observation suggests the likely existence of multiple isomers for these enzymes in kalmegh.

Proposed pathway for* ent*-LRD biosynthesis in kalmegh.

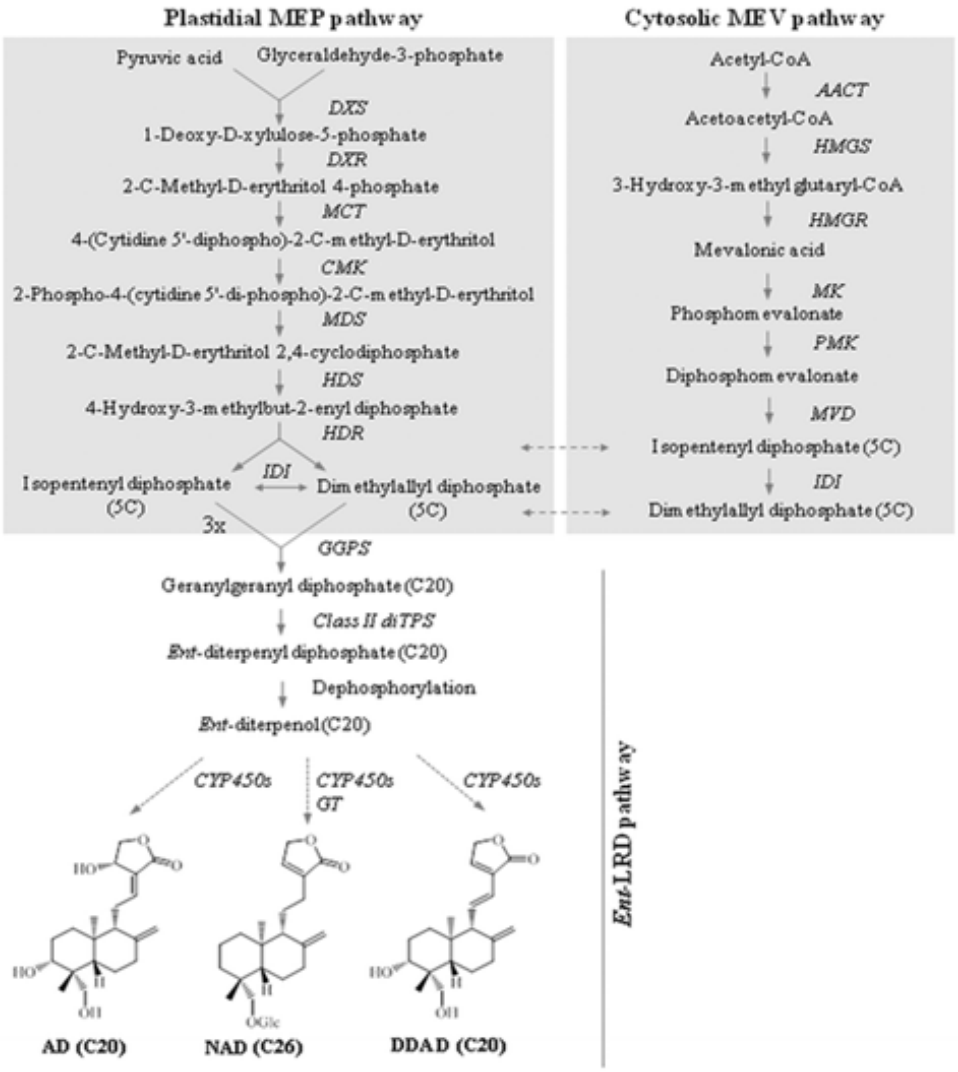


Figure 4
Putative transcripts of the pathway and corresponding enzymatic steps are shown. AD, andrographolide; NAD, neoandrographolide; DDAD, 14-deoxy-11, 12-didehydroandrographolide (Photo courtesy –Anchal Garg et al., 2015).

The second stage of diterpene biosynthesis involves head-to-tail condensation of three IPP and one DMAPP to a C20 compound geranylgeranyl diphosphate (GGPP). Thus, based on structures of kalmegh *ent*-LRDs, the involvement of class I and class II diTPSs, CYP450s and GTs enzymes in the biosynthesis of *ent*-LRDs was hypothesized. From kalmegh transcriptome database, three partial transcripts for the GGPS and three full-length transcripts for class II diTPSs with homology to the *ent*-copalyl diphosphate synthase (*ent*-CPS) are identified. Besides, several transcripts for CYP450s and GTs are also recognized. Transcripts that encode MEP pathway enzymes, GGPS, class II diTPS, CYP450 and GT, and preferentially expressed in leaf tissue are potential candidates for the biosynthesis of *ent*-LRDs in kalmegh. Although, two class I diTPSs with sequence similarity with *ent*-kaurene synthase are identified none of them preferentially expressed in leaf. Thus, their involvement in the biosynthesis of *ent*-LRD medicinal compounds in kalmegh may be excluded.

IDENTIFICATION OF SIMPLE SEQUENCE REPEATS IN DITERPENE BIOSYNTHETIC PATHWAY TRANSCRIPTS

Simple sequence repeats (SSRs) are often considered most efficient and reliable molecular markers for detecting genetic variations in plants[125]. A total of 16,485 potential SSRs were identified in 13,805 leaf transcripts whereas, 15,911 SSRs were detected in 13,213 root transcripts. Moreover, 2194 leaf and 2200 root transcripts were detected with more than one SSRs. Di-nucleotide repeats were the most abundant SSRs in leaf and root transcripts with 5194 and 5023 SSRs, respectively. The numbers of compound SSRs were 1877 and 1895 in leaf and root transcripts, respectively. Interestingly, several SSRs were also identified in transcripts of the specialized metabolic pathways, including terpenes and phenylpropanoids. SSRs were detected for the transcripts of the MEP pathway enzymes (DXS, MDS and HDR), GGPS and class II diTPSs (ApCPS2, ApCPS3). These SSRs could be useful in genotyping cultivars and developing specific chemotypes of kalmegh following marker-assisted selection.

IDENTIFICATION AND ANALYSIS OF DITERPENE SYNTHASES

Annotation of the kalmegh transcriptome revealed three diTPSs that showed close phylogenetic relationship with the dicotyledons monofunctional class II diTPSs of *ent*-CPP product specificity. These are ApCPS1 (ApU55291), ApCPS2 (ApU48901) and ApCPS3 (ApU53774). Similar to class II diTPSs, the highly conserved DXDD motif that is essential for the protonation-initiated cyclization of GGPP was identified in ApCPS1, ApCPS2 and ApCPS3, following multiple sequence alignment. Sequence analysis revealed that *ApCPS1*, *ApCPS2* and *ApCPS3* encode for 832-, 817- and 797- amino acids proteins with calculated molecular masses of 95.45, 93.43 and 90.81 kD, respectively. At the amino acid sequence level, ApCPS1 shared 55.2 and 57.21 % identities with ApCPS2 and ApCPS3, respectively. However, ApCPS2 shared 63.36 % amino acid identity with ApCPS3. Like other plant diTPSs, N-terminal transit peptides for the chloroplast localization were recognised in *ApCPS1*, *ApCPS2* and *ApCPS3*. But these exhibited dissimilar expression patterns in leaf and root tissues. The transcripts levels of *ApCPS1* were comparable in leaf and root tissues. However, *ApCPS2* showed high level of transcript accumulation in leaf and low level of transcript accumulation in root. *ApCPS3* transcripts are present at very high level in root and at very low level in leaf. This divergent expression pattern of *ApCPS1*, *ApCPS2* and *ApCPS3* specied their role in different diterpene metabolic pathways of kalmegh, although, their involvement in same biosynthetic pathway with functional redundancy cannot be completely excluded. In order to determine potential functions of *ApCPS1*, *ApCPS2* and *ApCPS3* in kalmegh, transcripts levels were analysed to correlate transcript expression with metabolite accumulation pattern, the level of andrographolide, the most abundant *ent*-LRD of kalmegh, was determined in plant organs and during seedling developmental ages following HPLC analysis. Maximum transcript level for *ApCPS1* was detected in stem (4.03-fold), followed by seedlings at cotyledonary leaf stage (CLS, 2.79-fold) as compared to germinating seeds (GS). *ApCPS1* transcript was also detected during seed germination. For the biosynthesis of phytohormone gibberellin (GA) *ent*-CPP serves as precursor which is known to promote seed germination, seedling development and stem elongation in plant species [128, 129, 126,127,] In contrast to *ApCPS1*, *ApCPS2* transcript expression was maximum in leaf (104.34-fold), followed by stem (14.19-fold) as compared to GS. However, very low level of *ApCPS2* transcript was detected during seed germination and in seedlings at the CLS stage, as compared to leaf and stem. Based on the transcript expression and *ent*-LRD metabolite accumulation patterns in plant organs and during seedling developmental ages, the role of *ApCPS2* in tissue-specific accumulation of medicinal *ent*-LRDs was anticipated. Thus, it is hypothesized this function of *ApCPS3* because class II diTPSs are known to play role in root phytoalexin biosynthesis in plants [130–132]. Moreover, kalmegh transcripts putatively encoding momilactone-A synthase, a phytoalexin biosynthetic pathway enzyme[133], also expressed at high level in roots.

ELEMENTAL ANALYSIS OF ANDROGRAPHIS PANICULATA

Elemental Analysis of plant samples has shown that the plant sample is a rich source of potassium, calcium, Magnesium, iron, aluminum, sodium and manganese are the chief constituents of the plant. Potassium has 14527 part per million; calcium has 3229 part per million. Very important constituent of the extracellular fluid is Potassium which is the principal intracellular cation, diuretic, ionic balance of the human body and maintains tissue excitability. Calcium (Ca) imparts strength and rigidity to bones and teeth. Calcium ions

are also needed in neuromuscular transmission, excitability of nerves, and normal excitability of heart, clotting of blood and promoting muscular contraction. The concentration of sodium is less i.e. 94 ppm (in wild), 96.2ppm (in cultivated). Sodium and potassium help in formation of gastric juice in stomach[134]. Iron (Fe) and zinc is used to make tendons and ligaments and is important for maintaining healthy immune system. Iron is essential for blood as it is an essential part of haemoglobin. Its deficiency can cause anaemia. Aluminum (Al) is now thought to be involved in action of a small number of enzymes. Magnesium (Mg) prevents from some heart disorders and high blood pressure and is associated with improved lung function. It helps in absorbing calcium and phosphorus. It is essential to control insulin levels in blood and is injected in veins in acute heart or asthma attack situations. Magnesium is effective in treating numerous heart/lung diseases. Trace elements such as Manganese, Iron and Zinc are essential in enzymes metabolism. The concentration of zinc is found 67 ppm in both the plant sample. Zinc (Zn) help in growth and repair of body tissues.[135]Among the trace elements the concentration of Molybdenum is found 264 parts per billion. The concentration of selenium varies 313 (wild), to 412 (cultivated) ppb. It showed that the plant holds tremendous promise in providing the variable secondary metabolites and mineral supply that could enhance the curative process of ill health. This plant is suitable to meet the human body requirement as an important supplement[136] .The analysis of different elements in the both the plant sample of *Andrographis paniculata* indicates that the sample possesses same types of elements but in different concentrations. The variation in concentration can be accounted due to the locality factors viz. soil composition, moisture contents, topography aspects, solubility of minerals diffusion and osmosis traits of the plants. Hence, the difference in concentration of the various elements is attributed to the nature of the plant as well as its locality factors. Furthermore, this difference can also be attributed to the edaphic factors along with the forest management practices. The different quantities of different elements under the present physical conditions of wild and cultivated sites are not in consonance with each other. These inorganic elements play an important role in physiological process involved in human health.

SAFETY

Burgos *et al* (2003)[51] found no subchronic testicular toxicity in male rats treated with the standardized dried extract of *Andrographis paniculata* as evaluated by reproductive organ weight, testicular histology, ultrastructural analysis of leydig cells and testosterome levels after a period of 60 days treatment.In mice that received oral extracts of *Andrographis paniculata* (10kg body weight) once a day for seven days, could survive and none of the mice died. Heart, kidney, liver and spleen were found to be normal in these animals. When 500mg/kg of *Andrographis paniculata* were given daily for ten days to mice, there was no effect on growth, appetite and stool production. The animals were energetic and results of complete blood counts were normal. As with all herbs, some people will have an allergic reaction to *Andrographis paniculata*.[141]

CONCLUSION

The plant *A. paniculata* has been valued for treating various infectious diseases and which are highly showing preventative effects against ailments like liver damage, hyperglycemia, dysentery, cancer, pulmonary tuberculosis, AIDS, acute and common cold, flu, myocardial infarction, inflammation, blood clotting etc. Andrographolide, a diterpenoid lactone having a diversity of pharmacological effects specified in ayurveda, unani, sidhha and traditional chinese medicine system. This herb. It has no toxic effects but yet it found unsafe during the pregnancy. In addition to it a great number of pharmaceutical uses, of which andrographolide has some side effects like nausea, vomiting, loss of appetite which can only be seen upon overdosing. Therefore, researchers may further be undertaken to develop potent formulations consisting of *A. paniculata* and its isolated molecule, andrographolide by making use of novel herbal drug delivery systems like microparticles, vesicular systems or through complexation with lipid or other suitable novel carrier.

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CONFLICT OF INTEREST

The four authors (S. Elumalai, R. Banupriya, T. Sangeetha and S. Madhumathi) has declared that there is no conflict of interest with reference to this article.

CONTRIBUTION OF AUTHOR

The Corresponding author Dr. S. Elumalai was the brainchild who motivated to review the article on the medicinally important plant *A. paniculata* and made necessary corrections with the same. The Second and third author R.Banupriya and T.Sangeetha collected the necessary informations and wrote the review article. Followed by them, S.Madhumathi rendered the technical support.

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