ANDROGRAPHIS PANICULATA - A REVIEW ON THE BIOLOGICAL ACTIVITIES OF THE PLANT

G. DEORA

Department of Human Genetics, Guru Nanak Dev University, Amritsar -143005, Punjab, India.
Accepted Date: 30/06/2014; Published Date: 27/08/2014

Abstract: Medicinal plants have been used for centuries as remedies for human diseases and offer a new source of biologically active chemical compounds. Andrographis paniculata, highly reputed as “Kalmegh” and “King of Bitters”, is one of the important herbs comprising of several medicinal properties. Mostly leaves and roots are used for different medicinal purposes. Diterpenoids and flavonoids are the main chemical constituents of A. paniculata which are believed to be responsible for the most biological activities of this plant. Medicinal properties of A. paniculata include its activities as anti-thrombotic, anti-hypertensive, anti-diarrhoeal, immune stimulatory, anti-malarial, anti-human immunodeficiency virus (HIV), anti-diabetic, analgesic, anti-pyretic, anti-hyperlipidemic, hepato-protective, anti-bacterial, anti-fungal, anti-cancer, anti-snakebite, anti-viral, anti-protozoal, cardio-protective, anti-inflammatory, anti-oxidant, gastro-protective and cerebro-protective. The present review focuses on the various biological activities of A. paniculata from the times when the different plant parts were eaten as dietary supplements, to the use of crude extracts in various studies using In vitro and in vivo models, and further to the extraction of different bioactive constituents and to study mechanisms of action of these different bioactive constituents on different cell signalling pathways, in context to various diseased conditions.

Keywords: Andrographis Paniculata, Kalmegh, King of Bitters

Corresponding Author: MR. GAURAV DEORA

Access Online On:
www.ijprbs.com

How to Cite This Article:
Deora G, IJPRBS, 2014; Volume 3(4): 263-283

Available Online at www.ijprbs.com
INTRODUCTION

Ayurveda, a combination of the Sanskrit words *ayu* meaning longevity and *veda* meaning knowledge, is the traditional medical system that has been practiced in India from more than 5000 years \(^1\). Ayurveda uses many herbal extracts for the treatment of variety of diseases. According to the World Health Organization, about 80% of the populations in many third world countries still use traditional medicine for their primary health care, due to poverty and lack of access to modern medicine \(^2\). Medicinal plants have been used for centuries as remedies for human diseases and offer a new source of biologically active chemical compounds. Medicinal plants are the richest bio-resources of drugs of traditional medicinal systems, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceuticals, intermediate and chemical entitled for synthetic drugs \(^3\). It has been estimated that 14 - 28% of higher plant species are used medicinally and that 74% of pharmacologically active plant derived components were discovered after following up on ethno medicinal use of the plants \(^4\). Out of the several hundred thousand medicinal plant species around the globe, only a small portion has been investigated both phytochemically and pharmacologically \(^5\). A number of evidences have been accumulated to demonstrate promising potential of medicinal plants as therapeutic agents.

*Andrographis paniculata*, highly reputed as “Kalmegh” and “King of Bitters”, is one of the important herbs comprising of several medicinal properties. *A. paniculata* is a well known traditional medicinal plant species with a bright economic horizon belonging to *Acanthaceae* family, found throughout Southeast Asia \(^6\). It is also referred to as the 'bile of earth' since it is one of the most bitter plants that are used in traditional medicine \(^7\). The bitterness of *A. paniculata* is related with its various pharmacological properties. Mostly leaves and roots are used for different medicinal purposes. The Indian Pharmacopoeia narrates that it is a predominant constituent of atleast 26 Ayurvedic formulations \(^7\).

**Synonyms:** *A. paniculata* Wall ex. Nees\(^8\), *Justicia latebrosa* Russel ex Wall., *J. Paniculata* Burm. f., *J. Stricta* Lam. Ex Steud. \(^9\).

**Common names:** Kalmegh, Kalafath, Kan-jang, Alui, Charita, Cherota, Chiraita, Cheretta, Kariyat, Green chiretta, Halviva, Kreat, Sinta, Rice bitters, Sambilata, Sambiloto, Andrographidis, Kraut \(^10\-\(^15\).
**Taxonomic hierarchy**

Kingdom : Plantae  
Division : Angiospermae  
Class : Dicotyledoneae  
Order : Tubiflorae  
Family : Acanthaceae  
Genus : Andrographis  
Species : *paniculata* Nees

**BIOACTIVE CONSTITUENTS OF A. *PANICULATA*:** The medicinal value of plants lies in some chemical substances that produce a definite physiologic action on the human body. The most important of these bioactive compounds of plants are alkaloids, flavonoids, tannins and phenolic compounds. Flavones, flavonoids and flavonols are phenolic structure with one carbonyl group. They are synthesized by plants in response to microbial infection and are often found effective in vitro as antimicrobial substance against a wide array of microorganisms and are a major group of compounds that act as primary antioxidants or free radical scavengers. Tannins are polymeric phenolic substances possessing the astringent property. These compounds are soluble in water, alcohol and acetone and give precipitates with proteins.

The phytochemical tests on *A. paniculata* revealed the presence of glycosides, saponins, tannins and alkaloids, but not of anthraquinones. Plant is very rich in chlorophyte. Diterpenoids and flavonoids are the main chemical constituents of *A. paniculata* which are believed to be responsible for the most biological activities of this plant. Active compounds extracted with ethanol or methanol from the whole plant, leaf and stem include over 20 diterpenoids and over ten flavonoids have been reported from *A.*
paniculata\textsuperscript{25, 26}. Structures of some major diterpenoids and flavonoids are shown in figure 1 and 2.

Andrographolide (C\textsubscript{20}H\textsubscript{30}O\textsubscript{5}) is the major diterpenoid in A. paniculata, making up about 4\%, 0.8-1.2\% and 0.5-6\% in dried whole plant, stem and leaf extracts respectively \textsuperscript{24, 27}. Diterpenic constituents present in A. paniculata are andrographolide, 14-deoxy-11,12-didehydroandrographolide, 14-deoxyandrographolide, 3,14-dideoxyandrographolide, 14-deoxy-12-hydroxyandrographolide, neandrographolide, 14-deoxyandrographolide \textsuperscript{28}. The roots give flavones apigenin-7,4-dio-O-methyl ether, 5-hydroxy-7,8,2',3'-tetramethoxyflavone, andrographin and panicolin and α-sitosterol \textsuperscript{29, 30}. Leaves contain homoandrographolide, andrographosterol and andrographone. Leaves contain two bitter substances lactone “andrographolide” and “kalmeghin”. Kalmeghin is the active principle that contains 0.6\% alkaloid of the crude plant. Andrographolide is abundant in leaves and can be easily isolated from the crude plant extracts as crystalline solid\textsuperscript{31, 32}.

![FIGURE 1: STRUCTURES OF SOME OF THE DITERPENOIDs PRESENT IN ANDROGRAPHIS PANICULATA](image-url)
POTENTIAL BENEFICIAL EFFECTS OF A. PANICULATA: A. paniculata is a well known medicinal plant of Ayurveda with various pharmacological as well as medicinal properties which include its activities as anti-thrombotic 33, anti-hypertensive 34, anti-diarrhoeal 35, immune stimulatory 36, 37, anti-malarial 38, 39, anti-human immunodeficiency virus (HIV) 40, 41, anti-diabetic 42-47, analgesic 43, anti-pyretic 43, anti-hyperlipidemic 46, hepato-protective 48-52, anti-bacterial 7, 43, 53-58, anti-fungal 55, anti-cancer 43, 59-69, anti-snakebite 70, 71, anti-viral 43, 72, anti/protozoal 73, cardio-protective 74, anti-inflammatory 43, 75-80, anti-oxidant 55, 56, 81, 82, gastro-protective 82 and cerebro-protective 83, 84. Due to its “blood purifying” activity it is recommended for use in cases of leprosy, gonorrhea, scabies, boils, skin eruptions and chronic and seasonal fevers 85. The leaves of A. paniculata are used in the treatment of infectious diseases 7. Andrographolide and related compounds were investigated for their pharmacological properties and all showed at least some degree of anti-pyretic, anti-malarial and anti-inflammatory activity 86-88. A study reported the antioxidant activity of A. paniculata using both in vitro and in vivo systems of whole plant extracts 89. It was been reported that Andrographis benefits for preventing heart diseases, helps protecting the liver diseases, stimulates gall bladder contraction 33, 42, 90. The majority of work done so far has used the roots and leaves of A. paniculata.
Anti oxidant activity: Oxidative stress of free radicals, usually resulting from deficient natural anti-oxidant defences \(^9\) has been implicated in the pathogenesis of a wide variety of clinical disorders, such as degenerative diseases \(^9\), aging \(^9\) and progressive impairment of the immune function \(^9\), mutagenesis, cancer, atherosclerosis, cardiovascular diseases, degenerative disorders and aging process \(^95-97\). Thus anti-oxidants have an important role in the prevention or treatment of these diseased conditions.

Several studies on the anti-oxidant activities of *A. paniculata* in various diseased conditions demonstrated the inhibition of nitric oxide (NO), lipid peroxide (LPO), superoxide dismutase (SOD) \(^42, 89, 98\). The aqueous, ethanol and methanol extracts of *A. paniculata* have been shown to display significant scavenging activities towards 1,1-diphenyl-2-picrylhydrazyl (DPPH), hydroxyl radical, hydrogen peroxide and nitric oxide in cell-free systems \(^42, 48, 98, 99\).

Hepato protective potential: In ayurvedic medicine, there are 26 different remedies containing *A. paniculata* to treat liver diseases. The effects of the aqueous extract of *A. paniculata* on the antioxidant defence system in liver-lymphoma bearing AKP mice have been reported \(^62\). The hepatoprotective action of andrographolide is related to the activity of certain metabolic enzymes. The inhibitory effect of plant extract and andrographolide on hepatic cytochrome P450s (CYPs) activities using rat and human liver microsomes has also been reported \(^49\). Administration of *A. paniculata* prevented hexachlorocyclohexane induced increase in activities of γ-glutamyl transpeptidase, glutathione-S-transferase and lipidperoxidation in mouse liver indicates antioxidant potential and hepatoprotective effect of *A. paniculata* \(^48, 100\). *A. paniculata* significantly increased the levels of acid-soluble sulfhydryl content, cytochrome P450 (CYP450), cytochrome P450 reductase, cytochrome b5 reductase, glutathione S-transferase and superoxide dismutase at both doses; while significant increase in the levels of catalase, glutathione peroxidase and glutathione reductase were observed only at higher doses to mice \(^98\). Andrographolide significantly induced CYP1A1 and CYP1A2 mRNA expression in cultures of mouse hepatocytes and acted synergistically with CYP1A inducers \(^101\). Hepatoprotective effects of the crude alcohol extract of leaves against CCl4-induced liver damage have also been reported \(^102\).

The hepatoprotective activity of methanolic extract of *A. paniculata* was evaluated against paracetamol induced (500mg/kg) hepatic damage in mice. The extracts at doses of 10mg/kg and 100mg/kg were orally administered at 24 and 72 hours time interval in each group. Histological analysis of the liver and the liver protein content indicates that the crude extracts of *A. paniculata* at both doses exhibited a significant protective effect in the liver morphology of the paracetamol induced hepatotoxicity in mice. There was
also a significant decrease in the liver protein content of the hepatotoxic mice after the treatments. Further, thin layer chromatography confirmed the presence of active compound, diterpene lactone or andrographolide which has contributed to the hepatoprotective activity of *A. paniculata* 51. Hepatoprotective study of andrographolide (the major active diterpenoid lactone of the plant *A. paniculata*) was done on acute hepatitis induced rats by a single dose of galactosamine (800mg/kg) and paracetamol (3g/kg). Pre-treatment and post-treatment of rats at different time intervals with different doses of andrographolide in the two experimental models of hepatotoxicity lead to complete normalisation of toxin-induced increase in the levels of all the five biochemical parameters and significantly ameliorated toxin-induced histopathological changes in the livers of experimental rats 103.

**Anti diabetic property:** Ethanol extract of *A. paniculata* administered orally twice daily for 14 days to streptozotocin-induced diabetic rats significantly reduced fasting serum glucose and increased body weight in a dose-dependent manner. The extract also significantly lowered levels of thiobarbituric acid-reactive substances in liver and kidney compared to vehicle-treated rats, while significantly increasing the activity of superoxide dismutase and catalase enzymes and hepatic glutathione concentrations in diabetic rats 42. Andrographolide appears to dose-dependently reduce plasma glucose concentration in streptozotocin-induced diabetic rats and normal rats, with a more marked effect in normal rats than in diabetic rats. Andrographolide also attenuated the increase in plasma glucose in response to an intravenous glucose challenge in normal rats and enhances the uptake of radioactive glucose by isolated soleus muscle of streptozotocin-diabetic rats in a concentration-dependent manner. Repeated intravenous administration of andrographolide in diabetic rats for three days resulted in an increase in mRNA and protein levels of glucose transporter (GLUT4) in the soleus muscle, an indication that the glucose-lowering effect of andrographolide could be due to better glucose utilization by skeletal muscle 104. Extensive research concluded that the hypoglycemic effect of *A. paniculata* is due to insulin release from pancreatic cells through ATP-sensitive potassium channels, similar to other insulinotropic anti-diabetic agents 45 or inhibition of alpha-glucosidase and alpha-amylase enzyme could be the mechanism by which the ethanol extract of *A. paniculata* and andrographolide produce hypoglycemic effect 44. Water extract of *A. paniculata* significantly prevents orally administered glucose-induced hyperglycemia in nondiabetic rabbits without affecting epinephrine-induced hyperglycemia. Chronic administration of the extract for six weeks also showed no effect on fasting blood glucose level 105.

**Cardio protective potential:** The hydroalcoholic extract of *A. paniculata* possesses antioxidant activity against oxidative alterations in myocardium and confer significant
cardio-protective activity by helping in retaining the cardiac function in a normal manner. Hydroalcoholic extract of *A. paniculata* prevented isoproterenol induced increase in lipid peroxidation and increased the activities of antioxidant enzymes viz. Super oxide dismutase, catalase, glutathione peroxidise and the levels of reduced glutathione in hearts. In addition, the extract also prevented the leakage of lactate dehydrogenase from heart and salvages the heart from isoproterenol induced myocardial ischemic injury. Aquous extract of *A. paniculata* produced a dose-dependent fall in systolic blood pressure of both spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto rats, with a corresponding significant decrease in plasma angiotensin converting enzyme (ACE) activity and lipid peroxidation in kidneys in extract-treated SHRs. The hypotensive effect of n-butanol and aqueous fractions of the crude water extract is antagonized or attenuated by phentolamine, hexamethonium, pyrilamine and cimetidine, but not by propranolol, atropine, or captopril.

**Anti snakebite activity:** *A. paniculata* plant extracts were effective in neutralizing the toxic effects of the D. Russellii venom. The methanolic extracts of *A. paniculata* and *Aristolochia indica* plants were reported to neutralize the D. Russellii venom induced lethal activity by incubating the venom and plant extracts prior to testing by pre-incubation method. About 0.15mg of *A. paniculata* and 0.14mg of *A. indica* plant extracts were able to completely neutralize the lethal activity of 2LD50 of D. Russellii venom. Various pharmacological activities including oedema, haemorrhagic, coagulant, fibrinolytic and phospholipase activities were significantly neutralized by both the plant extracts.

**Anti cancer, Anti inflammatory and immune stimulatory activities:** In vitro studies have shown that the flavonoid activities suppressed the genetic expression of neutrophils, an inflammatory agent and andrographolide, helps to stop the clumping of blood platelets which is the clotting process that can lead to heart attacks. Immunostimulatory activity of *A. paniculata* is evidenced by increased proliferation of lymphocytes and production of interleukin 2 in vitro. *A. paniculata* 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. Laboratory tests conducted in Buffalo also demonstrated that *A. paniculata* inhibited the growth of human breast cancer cells at levels similar to the drug tamoxifen. The consumption of the infused aerial parts of *A. paniculata*, alongside with meals (as blood tonic), is being encouraged, as it is believed to enhance immune system functions such as production of white blood cells (scavengers of bacteria and other foreign matter), release of interferon and increase the activity of the lymph system and to prevent or cure infective and degenerative diseases.
Andrographolide exhibits multiple pharmacological properties and is a potential chemotherapeutic agent. Andrographolide contains α-alkylidene γ-butyrolactone moiety and three hydroxyls at C-3, C-19 and C-14 responsible for the cytotoxic activities of andrographolide against many cancer cell lines. Recent studies have indicated that andrographolide inhibits tumor growth by inducing cell cycle arrest or apoptosis in various types of cancer cells. Recently, a study confirmed that andrographolide enhances NF-κB subunit p65 Ser536 dephosphorylation through neutral sphingomyelinase (nSMase)-mediated ceramide formation in VSMCs, involving an increase in cyclic GMP/PKG, followed by the inhibition of the p38MAPK/HO-1/NF-κBERK2 cascade in activated platelets. My own study showed that methanolic and water extracts significantly inhibited the proliferation of C6 glioma cells in a concentration dependent manner.

**Anti fertility activity:** It has also been reported that administration of *A. paniculata* resulted in abortion in pregnant rabbits. Intraperitoneal injection of the decoction of aerial parts to female albino mice was reported to prevent implantation and caused abortion at different gestation periods. Early pregnancy was also terminated by intramuscular, subcutaneous and intravenous administration. In addition, the herb is reported to suppress growth of human placental chorionic trophoblastic cells *in vitro*. A study reported that the dried extract of *A. paniculata* induces uterine relaxation by blocking voltage-sensitive calcium channels. Early reports of oral administration of powdered stem indicated an antifertility effect in male Wistar mice, but no impact on fertility in female mice. Dry leaf powder was administered to male albino rats (20mg daily for 60 days) and reported inhibition of spermatogenesis, degenerative changes in the seminiferous tubules, regression of Leydig cells and regressive and/or degenerative changes in the epididymis, seminal vesicle, ventral prostate and coagulating glands. Andrographolide also produced similar results when orally administered to male Wistar albino rats for 48 days. Sperm count and sperm motility were decreased and sperm abnormalities were noted.

**Anti microbial activity:** The crude aqueous extract of leaves exhibited significant antimicrobial activity against gram-positive *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA) and gram-negative *Pseudomonas aeruginosa*, but had no activity against *Escherichia coli* or *Klebsiella pneumonia*. The ethanol extract was also devoid of significant activity against enterohemorrhagic strains of *E. Coli*. The chloroform extract completely inhibited malarial parasitic growth within 24 hours of incubation at a concentration of 0.05mg/mL. The same inhibition was achieved in 48 hours with methanol extract at a concentration of 2.5mg/mL. The methanol extract significantly inhibited *Plasmodium falciparum* at a 50-percent inhibitory concentration (IC50) of
7.2μg/mL  39. 1,8-dihydroxy-3,7-dimethoxyxanthone,  4,8-dihydroxy-2,7-dimethoxyxanthone,  
1,2-dihydroxy-6,8-dimethoxyxanthone and 3,7,8-trimethoxy-1-hydroxy-xanthone exhibited  
antiprotozoal activity against Trypanosoma brucei, Trypanosoma cruzi and Leishmania  
infantum  73. Water extract of the leaves exhibited filaricidal activity, both in vitro and in  
dogs  120. A. paniculata was reported to cure 91 percent of acute bacillary dysentery  
cases which was achieved with a compound tablet containing andrographolide and  
neandrographolide (at a ratio of 7:3)  11. A similar study reported significant antibacterial  
activity of an aqueous extract due to andrographolides and arabinogalactan proteins  53.

**Anti viral property:** Andrographolide, neandrographolide and 14-deoxy-11,12didehydroandrographolide are reported to be viricidal against herpes simplex virus 1 (HSV-1) without having any significant cytotoxicity at viricidal concentrations  121. An in vitro study investigated the anti-influenza activity of A. paniculata in canine kidney cell line as well as mice infected with H1N1, H9N2 or H5N1. A newly synthesized andrographolide derivative 14-α-lipoyl andrographolide was more effective against avian influenza A and human influenza A in vitro than andrographolide  72. The aqueous extract of A. paniculata against anti-human immunodeficiency virus (HIV) was studied by testing the inhibitory activities against HIV in the H9 cell line  122. The anti-HIV activity of the hexane and methanol extracts of A. paniculata was tested. Seven compounds, namely andrographolide, bis-andrographolide, 14-deoxy-11,12-didehydroandrographolide, andrograpanin, 14-deoxyandrographolide, 5-hydroxy-7,8-dimethoxyflavanone and 5-hydroxy-7,8-dimethoxyflavone. Andrographolide and 14-deoxy-11, 12-didehydroandrographolide showed anti-HIV activity  123.

**CONCLUSION:** With such diverse biological activities A. paniculata is much of like a wonder  
plant. The need of the hour now is to utilize the huge potential which this plant holds.  
Future studies need to shift their focus onto how this plant can be used as a dietary  
supplement for everyone by subtracting anti-fertility agents from the plant which gives it  
a contradictable status. Further it is required to move one step forward from in vitro  
and in vivo models to clinical trials to study and confirm the effect of the bioactive  
components isolated from this plant, in context to various diseased conditions.

**ACKNOWLEDGEMENT:** The author is highly thankful to Dr. Vasudha Sambyal, Professor,  
Department of Human Genetics, Guru Nanak University, Amritsar, Punjab for her timely  
guidance, valuable suggestions and constant motivation in writing this review paper.

**REFERENCES**

1. Valiathan MS and Thatte U: Ayurveda: the time to experiment. International journal of  
Ayurveda research 2010; 1: 3.


15. Farnsworth NF: NAPRALERT database. Chicago, University of Illinois at Chicago, IL, January 28, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).


34. Ahmad M and Asmawi MZ: Some pharmacological effects of aqueous extract of *Andrographis paniculata* Nees. Proceedings of the International Conference on the Use of Traditional Medicine and Other Natural Products in Health-Care, School of Pharmaceutical Sciences, Penang, Malaysia, 1993: 573.


Available Online at www.ijprbs.com
