

Andrographis paniculata: A Review of its Traditional Uses, Phytochemistry and Pharmacology

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Abstract

Objective: Plants have been effectively used in traditional medicines for centuries. The present review aims at compiling vast pharmacological applications to comprehend and synthesize the potential image of Andrographis paniculata as a multipurpose medicinal agent.

Key findings: The aerial part of the plant contains a large number of chemical constituents, mainly lactones, diterpenoids, diterpene glycosides, flavonoids and flavonoid glycosides. It has multiple pharmacological properties such as antibacterial, hepatoprotective activity, anti-cancer, antitumor, hypoglycemic, immunomodulatory and hypotensive activities.

Conclusions: The plant is widely cultivated and its importance as a medicinal plant is growing up with stronger reports in support of its multifarious therapeutic uses. Taking great concern of the useful benefits of the plant, it can be advocated as a safe, highly important medicinal plant for mankind.

Keywords: Andrographis paniculata, antibacterial, hepatoprotective, anti-HIV, anticancer, antitumor, hypoglycemic, immunomodulatory, hypotensive.

Introduction

Over the past twenty years, interest in medicinal plants has grown enormously from the use of herbal products as natural cosmetics and for self-medication by the general public to the scientific investigations of plants for their biological effects in human beings. Beyond this pharmaceutical approach to plants, there is a wide tendency to utilize herbal products to supplement the diet, mainly with the intention of improving the quality of life and preventing the diseases of elderly people. India has been identified as a major resourceful area in the traditional and alternative medicines globally.

Andrographis paniculata (Burm.f.) Wall. ex Nees., (Family-Acanthaceae) (English name-King of Bitters, Tamil name-Nilavempu) is an annual herbaceous plant and is extensively cultivated in Southern Asia, China and some parts of Europe. In traditional medicine, A. paniculata is widely used to get rid of body heat, dispel toxins from the body; prevent common cold, upper respiratory tract infections including sinusitis and fever [1] and as an antidote against poisons of snakes and insects [2]. The plant has been reported to exhibit various mode of biological activities in vivo as well as in vitro viz., antibacterial [3-7], antiviral [8], anti-inflammatory [9], anti HIV (Human immunodeficiency virus) [10], immunomodulating/ immunostimulatory [11] and anticancer [12,13]. The plant showed potential therapeutic action in curing liver disorders, common cough and colds in human [14]. The characteristic secondary metabolites encountered in this plant have considerably enhanced its importance in the arena of medicinal plants.

Botanical description

Andrographis paniculata is an annual, branched, herbaceous plant erecting to a height of 30-110 cm in moist shady places. The stem is acutely quadrangular; much branched and can be broken easily due to its fragile texture. Leaves are simple, opposite, glabrous, lanceolate, 2-12 cm long, 1-3 cm wide with acute entire margin. Inflorescence is terminal and axillary in panicle, 10-30 mm long with small bract and short pedicel. The flowers possess calyx with 5 sepals which are small and linear. Corolla tubes are narrow, about 6 mm long, bilabiate, upper lip oblong, white with a yellowish top, whereas the lower tips are broadly cuneate, 3-lobed, white with violet markings. Stamens 2, inserted in the throat, anther basally bearded. Ovary superior, 2-celled with exerted style. Capsule of the herb is erect, linear-oblong, 1-2 cm long, compressed, longitudinally furrowed on broad faces with thin glandular hairs. Seeds are very small [15,16]. Traditional uses Andrographis paniculata, a traditional medicinal plant, has been used for centuries to successfully treat respiratory diseases, skin infections, herpes, dysentery, fever, sore throat, lower urinary tract infections, to reduce inflammation and to stop diarrhoea [17]. Clinically, the use of this herb is reported in contemporary and ancient Chinese writings [18]. In Traditional Chinese Medicine, Andrographis paniculata is a bitter and 'cold property' herb. It is used in the treatment of 'hot' conditions such as acute infections and fever, including throat infection, pneumonia, tonsillitis, dysentery, gastroenteritis and pyelonephritis [19-21]. It is also prescribed for snakebite [22,23]. It is used in Malaysian folk medicine for diabetes and hypertension [24-26]. Yeung et al. [27] reported that A. paniculata had pharmacological properties which include antibacterial, immunological, antivenomous and antithrombotic properties. More recently, A. paniculata has been used in the treatment of chronic bronchitis, administered via aquapuncture, i.e. the injection of an infusion into acupuncture points [22]. In Ayurvedic medicine, it is used as a bitter tonic and stomachic, for diabetes, debility, hepatitis and as an anthelmintic [21]. A. paniculata extract has been used in different forms, such as tablet or injection. In China, in tablets form it has different names:

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"Kan Jang" tablets, "Chuanxinlian" tablets, "Xiaoyan Lidan" tablets and "Chuanxinlian antiphologistic" Pills [28]. The injection forms are "Yamdepieng" and "Chuanxinlian Ruangas" [29]. In Indian pharmacopoeia, 26 Ayurvedic formulations are widely used [30]. In the Unani system of medicine it is considered aperients, antiinflammatory, emollient, astringent, diuretic, emmenagogue, gastric and liver tonic, carminative, antihelminthic, and antipyretic. 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 [31].

The knowledge on the benefits of Andrographis paniculata for human health has also led to its use in livestock production in Thailand. A. paniculata or mixtures of A. paniculata and other plants have been used to treat poultry in broiler production instead of antibiotics on several farms. Farmers believe that A. paniculata reduce mortality that is caused by digestive tract infections and respiratory tract diseases but little systematic research has been reported [32]. Phytochemistry The plant contains bitter glucosides: andrographolide, panaculoside, flavonoids, andrographonin, panicalin, neoandrographolide, apigenin 7-4-dimethyl ether. The plant contains diterpenoids-14-deoxy-11-oxoandrographolide; 14-deoxy-11,12-didehydroandrographolide,neoan drogra-pholide, 14-deoxyandrographolide and andrographolide. The roots gave 5-hydroxy-7,8,2'3'-tetramethoxyflavone, andrographonin, flavonesapigenin-7,4'-di-O-methyl ether, panicolin and α -sitosterol. Leaves contain andrographosterol, homoandrographolide and andrographone. Whole plant, leaves and root contains a furonoid diterpine Andrographolide; 2',5-dihydroxy-7,8-dimethoxyflavone-2'-o-β-(D)-Glucoside, 3β-hydroxy-5-stigmasta -9(11),22(23)-diene,panicolin,d iterpeneglucoside-neoandrographolide,flavone-5-hydroxy-7,8,2',3' andrographin, 5-hydroxy-7,8-flavanone, tetramethoxyflavone, 7,4-dioxymethylether, mono-oxymethylwigthin, apigenin, deoxyandro-grapholide -19β-D-glucoside, flavone glucoside A, B, C, D, E and F(root), 5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-3,7,8,2'tetramethoxyflavone, 7-o-methylwogonin, α-sitosterol, apigenin-7,4'bitter di-omethylether, β-sitosterol glucoside, substances, myristic acids, carcrol, neoandrographolide, chlorogenic, pan icolide,eugenol,caffeic,hentriacontane, dicaffeoylquinic acids. tritricontane. 3,14-dideoxyandrographo-lide, andro-graphiside, ent-14 β-hydroxy-8(17),12-labadien-16,15-olide-3 β19-oxide part);oroxylinA,homoandro-grapholide,andrographone, (aerial α - β -unsaturated lactone (leaves); 14-deoxyandrographiside, wogonin, and ropanoside, 14-deoxy-12-methoxy and rographolide, 14deoxyandrographolide, andrograpanin, 14-deoxy-11-oxoandrograph olide,neoandrographolide,5-hydroxy-2,7,8-trimethoxyflavone,androg raphside,14-deoxy-11,12-didehydro androgra-pholide, 2',5-dihydroxy 7,8-dimethoxyflavone, 14-deoxyandrographoside (plant).

Structures of some phytoconstituents isolated from Andrographis paniculata (Figure 1)

Andrographolide is a colourless or light yellow crystal compound with a very bitter taste [33,34]. Deng et al. [19] reported that there are four lactones in Andrographis paniculata viz., (1) 14-deoxyandrographolide, which was also identified by Sangalungkarn et al. [35] and Garcia et al. [36] (2) andrographolide, (3) neoandrographolide (a non-bitter, C 3 O glucoside derivative of the major constituent andrographolide) and (4) 14-deoxy-11,12-di-dehydro-andrographolide which were also identified by Dhammaupakorn et al. [37]. Andrographolide and total lactone are the common names used in clinics for the active ingredients [19]. The other medicinal chemical principles are diterpenoids viz. 14-deoxyandrographolide, -19β -D-glucoside which has been isolated from the leaves [17,38]. Du et al. [39] separated andrographolide and neoandrographolide from the leaves of Andrographis paniculata using highspeed counter-current chromatography. The leaves of *A. paniculata* grown best in the tropical and subtropical areas of China and Southeast



Asia contain more than 2% andrographolide before the plant blooms and less than 0.5% afterwards. The content of andrographolide depends on both growing region and the collection time. The stem contains 0.1-0.4% of andrographolide [40]. The best harvesting time is early autumn [41]. The other active chemical constituents of Andrographis paniculata which have been identified so far include diterpene dimers [42] and flavonoids [43]. Quantitative HPLC analysis of andrographolide isolated from two different stages of life cycle of the plants also showed a wide range of phytoconstituents [44].

Pharmacognosy

The presence of important phytochemicals in *A. paniculata* make the plant useful for treating different ailments and have a potential of providing useful drugs of human use. The quantitative determination of pharmacognostic parameters will help for setting standards for crude drugs [45,46].

Antibacterial activity

The development of bacterial resistance to currently available antibiotics has made it necessary to search for new antibacterial agents. New sources, especially natural products from plants, are being investigated because medicinal plants have been widely used for treatment of many types of acute and chronic diseases and many plants with antimicrobial activity have been reported [47]. Within the recent years, infections have increased to a great extent and antibiotics resistance effects become an ever-increasing therapeutic problem [48]. Natural products of higher plants may possess a new source of antimicrobial agents with possibly novel mechanisms of action [49,50]. They are effective in the treatment of infectious diseases while simultaneously mitigating many of the side effects that are often associated with synthetic antimicrobials [51].

Therefore, it is of great interest to carry out a screening of these plants in order to validate their use in folk medicine and to reveal the active principle by isolation and characterisation of their constituents. Systematic screening of them may result in the discovery of novel active compounds against pathogenic organisms [52].

The plant Andrographis paniculata, is an antibacterial agent capable of counteracting the ill effects of pathogenic microbes [53-56]. 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. [57]. A similar conclusion was reached by Radha et al. [58] who found that petroleum ether, acetone, chloroform and methanol extracts of *A. paniculata* leaves and stems, exhibit significant antimicrobial potential against Enterococcus faecalis, Streptococcus pyogenes, Klebsiella pneumonia and Proteus vulgaris.

Abubacker and Vasantha [59] studied the antibacterial effect of ethanolic leaf extract of *A. paniculata* against Escherichia coli; Klebsiella pneumonia, Proteus vulgaris and Streptococcus pneumonia by disc diffusion method were identified. The results revealed that 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 is on par with standard antibiotics.

Non-polar (dichloromethane) and polar (methyl alcohol and aqueous) extracts of *A. paniculata* (whole plant) were evaluated for in vitro antibacterial activity against 12 skin disease causing bacterial strains (7 gram positive strains; Staphylococcus saprophyticus, Staphylococcus epidermis, Staphylococcus aureus, Streptococcus pyogenes, Bacillus anthracis, Micrococcus luteus, Enterococcus

faecalis) and 5 gram negative strains; Proteus mirabilis, Proteus vulgaris, Klebsiella pneumonia, Neisseria meningitis, Pseudomonas aeruginosa) using the disc diffusion method at three concentrations; 1000, 500, and 250 µg/disc respectively in order to ascertain its folkloric claim to treat skin infections. The extracts showed significant antibacterial activities against both the gram-positive and gram-negative bacterial strains tested. Highest significant antibacterial activity was exerted by the methyl alcohol extract against E. faecalis at 1000 µg/disc (24.00±0.00 mm) and the least activity by the dichloromethane extract against N. meningitis at 250 µg/disc (6.00±0.00 mm). The minimum inhibitory concentration ranged between 150 µg/ml and 300 µg/ml depending on microorganisms and various extracts [60]. Similar results were observed by Aniel Kumar and his coworkers against different grampositive (Staphylococcus aureus and Bacillus subtilis) and gramnegative (Escherichia coli, Klebsiella pneumonia and Proteus vulgaris) bacteria [61].

Misra et al. evaluated the ethanol extract of the aerial part of *A. paniculata* for antimicrobial activity against eleven bacterial strains. The results revealed that the ethanolic extract is potent in inhibiting bacterial growth of both gram-negative and gram-positive bacteria [4].

The antibacterial activity of the Hexane, Chloroform and Methanolic extracts of Andrographis paniculata was determined by Bobbarala et al. [62] using the well diffusion method and showed broad spectrum antibacterial activity against tested organisms. The growths of all bacterial pathogens were highly inhibited by methanolic extracts of Andrographis paniculata than chloroform and hexane extracts respectively. 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. In vitro screening of the aqueous extract of A. paniculata posses' potential antibacterial activity towards both gram-positive and gram-negative microorganisms [63]. The antimicrobial activity of aqueous extract of Andrographis paniculata/ 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 [3]. Similar work conducted by Chakraborty et al. on the aqueous extract of Andrographis paniculata is more effective against Staphylococcus aureus than Escherichia coli. Minimum inhibitory concentration (MIC) value of Andrographis paniculata is 0.0009 mg/ml against Staphylococcus aureus and 0.001mg/ml against Escherichia coli [64].

In a study conducted by Sukesh and his coworkers' considerable levels of antibacterial activity was reported against penicillin resistant Staphylococcus aureus MTCC 87 [65]. Similar studies were conducted by Hosamani et al. using chloroform, acetone, ethanol and aqueous extracts of *A. paniculata* against bacterial strains like Bacillus subtilis, Staphylococcus aureus, and Pseudomonas aeruginosa. Out of the four extract used, acetone and ethanol extracts were found to be highly active against Staphylococcus aureus and Bacillus subtilis [66]. Methanol extract of Andrographis paniculata was investigated for in vitro antimicrobial activity against pathogens namely Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa by disc diffusion method. *A. paniculata* (4 mg/disc) showed activity against S. epidermidis, K. pneumoniae and *E. coli* [67].

Aqueous and two ethanolic extracts of Andrographis paniculata and Andrographolide, an active principle of A. paniculata, were investigated for their antimicrobial activity against nine bacterial species in vitro using the disc diffusion method. It was discovered that neither the aqueous extract nor Andrographolide were bacteriostatic or bactericidal against S. typhimurium, E. coli, S. sonnei, S. aureus, P. aeruginosa, S. pneumoniae, S. pyogenes, L. pneumophila or B. pertussis but the two ethanolic extracts of *A. paniculata* were bacteriostatic against L. pneumophila and B. pertussis [68].

Investigations made by Xu et al. on the antibacterial activity using *A. paniculata* (methanolic and aqueous) extracts and authentic andrographolide against nine human bacterial pathogens gave evidences that authentic andrographolide did not show any activity. They concluded that the observed antimicrobial activity was due to other active principles present in the extracts that were used in the investigation [69].

Antioxidant activity

An antioxidant is a molecule capable of terminating the chain reactions that damage cells by removing free radical intermediates, and inhibit other oxidation reactions by thereby reducing stress responsible for many degenerative disorders. Andrographis paniculata Nees, a multipurpose tropical plant is believed to have antioxidant properties [54,55].

Verma and Vinayak compared the antioxidant effects of the aqueous extract on liver defense systems in lymphoma bearing mice. The aqueous extract significantly increased the activities of catalase, superoxide dismutase and glutathione-S-transferase enzymes and reduced lactate dehydrogenase activity [70]. Extracts prepared from cultivated A. paniculata and their active constituent andrographolide were evaluated for antioxidant, antioedema and analgesic activities. The results showed that the aqueous A. paniculata extract (A. paniculatawater) exhibited a greater antioxidant activity than the ethanol A. paniculata extract (A. paniculata-Ethanol) in all model systems tested. At a concentration of 50 µg/ml, the free radical scavenging xanthine oxidase inhibition and antilipid peroxidation activities for A. paniculata-water were 66.8%, 57.3% and 65.3%, respectively, and for A. paniculata-Ethanol were 57.8%, 52.6% and 34.2% repectively. It has been reported that A. paniculata-water was more potent than A. paniculata-Ethanol in antioxidant activities [71].

Hydroalcoholic extract of *A. paniculata* possesses antioxidant activity against oxidative alterations in myocardium and confer significant cardioprotective activity by helping in retaining the cardiac function in a normal manner [72].

Akowuah and his coworkers determined the content of andrographolide (AP) and 14-deoxy-11,12-dideoxyandrographolide (DIAP) in a pooled urine of rat obtained within 24 h after an oral dose of Andrographis paniculata leaf extract at 1 g/kg body weight. Cumulative urinary excretion of AP and DIAP in 24 h after oral administration of the extract was 0.88% and 1.61% of oral dose administered, respectively. The extract showed significant reduction (p < 0.05) of MDA levels and elevation of total antioxidant status in rat urine samples collected in 24 after oral administration [73].

A rapid method based on HPTLC and RP-HPLC with UV detection for quantitative determination of two major bioactive compounds in A. paniculata, andrographolide and 14-deoxy-11,12-didehydroandrographolide, is described. The recoveries of the two compounds were between 96.5–99.0% by HPTLC method and 98.1–99.2% by HPLC assay. The relative standard deviations of the two compounds ranged between 0.89–0.99 (intra-day) and 0.86–0.98 (inter-day) for the HPTLC method and 0.86–1.02 (intra-day) and

0.87–1.12 (inter-day) for HPLC method. The methods were used for routine analyses and to obtain relative amount of the two compounds in the leaves of the plant cultivated in different locations of Malaysia. The extracts and isolated compounds exhibited lipid peroxidation inhibition and free radical activities [74].

In a study, 5 μ M ABA and GA3 concentration were used to find the effect of these growth regulators on the andrographolide content and antioxidant potentials of Andrographis paniculata. The growth regulators were applied by means of foliar spray during morning hours. A significant enhancement in non-enzymatic antioxidant contents was observed in all sampling days in *A. paniculata* plants under ABA and GA3 treatments. Ascorbic acid and α -tocopherol content was increased significantly under the growth regulator treatments in leaves, stem and roots of A. paniculata. The activities of antioxidant enzymes such as ascorbate peroxidase, superoxide dismutase and catalase were increased by ABA and GA3 treatments in the leaves, stem and roots of *A. paniculata* plants. The HPLC analysis was used to quantify the andrographolide content in control and growth regulator treated plants. The growth regulators ABA and GA3 treated plants showed increased contents of andrographolide when compared to control [75].

Sharma et al. focused on the anti-oxidant potency of aqueous, methanol and ethanol extracts of Andrographis paniculata .The methanolic extracts of leaves of Andrographis paniculata showed promising anti-oxidant activity .Results suggest that the active anti-oxidant compounds are better extracted in methanol for Andrographis paniculata. Results also suggest that there is a direct co-relation between the total polyphenols extracted and anti-oxidant activity. Free radical scavenging potential of various extracts (methanol, ethanol and aqueous) of A. paniculata. In this method, ascorbic acid was used as a standard of determining reducing power. The methanol extract of the leaves of *A. paniculata* exhibited appreciable activity as compared to the aqueous and ethanol extracts, indicating that *A. paniculata* has promising free radical scavenging activity [76].

Prakash et al. [77] evaluated the in vitro antioxidant activities of leaf extract of Andrographis paniculata by three different in vitro models such as, Hydroxyl radical scavenging activity, FRAP method and total phenol estimation. The leaf extract of *A. paniculata* was found to more effective in the hydroxyl radical scavenging activity. The IC50 values of the leaf extract of *A. paniculata* and ascorbate were found to be 370µg/ml and 410µg/ml respectively. FRAP method of leaf extract and Ascorbate IC50 values were found to be 210 µg/ml and 50 µg/ml. In addition, the leaf extract of *A. paniculata* was found to contain a noticeable amount of total phenols (5.96 mg/g), which play a major role in controlling antioxidants. So, the in-vitro studies clearly showed that the leaf extract of *A. paniculata* has a significant antioxidant activity. It can be concluded that the free radical scavenging activity of the leaf extract of *A. paniculata* responsible for the therapeutic properties.

Anti-inflammatory activity

Shen et al. have established that the anti-inflammatory effect of Andrographolide could be explained by its ability to inhibit neutrophil adhesion/transmigration through suppression of Mac-1 upregulation. The inhibitory effect of Andrographolide on Mac-1 expression could be mediated by down regulation of ROS production via a PKC-dependent but calcium independent mechanism. As effective anti-adhesive and anti-transmigration drug at pharmacological concentrations (0.1 \pm 10 mM), Andrographolide may be useful for the improvement of inflammatory disorders by limiting the early phases of neutrophil infiltration [78].

The anti-inflammatory activity of chloroform extract of Andrographis paniculata stem was determined by Radhika and her coworkers using carrageenan induced rat hind paw oedema model for acute inflammation. Ibuprofen was used as a standard drug in this study. The chloroform extract of Andrographis paniculata stem showed statistically significant effect in 6th hour at a dose of 200mg/kg and the results were comparable with the standard anti-inflammatory drug Ibuprofen (10 mg/kg) (t = 64.06, p< 0.001) [79].

Iruretagoyena et al. showed that andrographolide is able to downmodulate both humoral and cellular adaptive immune responses. This molecule when used in vitro, was able to interfere with T cell proliferation and cytokine release in response to allogenic stimulation. These results were consistent with the observation that T cell activation by dendritic cells (DCs) was completely abolished by exposing dendritic cells to andrographolide during antigen pulse. This molecule was able to interfere with maturation of dendritic cells and with their ability to present antigens to T cells. Furthermore, in vivo immune responses such as antibody response to a thymus-dependent antigen and delayed-type hypersensitivity were drastically diminished in mice by andrographolide treatment. Finally, the ability of andrographolide to inhibit T cell activation was applied to interfere with the onset of experimental autoimmune encephalomyelitis (EAE), an inflammatory demyelinating disease of the central nervous system that is primarily mediated by CD4 T cells and serves as an animal model for human multiple sclerosis. Treatment with andrographolide was able to significantly reduce EAE symptoms in mice by inhibiting T cell and antibody responses directed to myelin antigens. Their data suggest that andrographolide is able to efficiently block T cell activation in vitro, as well as in vivo, a feature that could be useful for interfering with detrimental T cell responses [11].

An anti-inflammatory benefit of andrographolide by reduction of inducible nitric oxide synthase protein expression through prevention of the de novo protein synthesis and decreasing the protein stability through a post-transcriptional mechanism has been inferred [80,81]. Antihyperglycemic and hypoglycemic effects Aqueous extract of Andrographis 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 [82]. However, ethanol extract, administered orally twice daily for 14 days to streptozotocin induced diabetic rats significantly reduced 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 enzymes in diabetic rats [26]. An aqueous extract at a dose of 400 mg/kg body weight twice daily for two weeks to diabetic rats produced a 49.8-percent reduction in fasting serum triglyceride levels. This was greater than the 27.7-percent decline achieved with 500 mg/kg body weight metformin twice daily for 14 days [83]. Husen and his coworkers found that aqueous extract (50 mg/kg body weight) given to streptozotocin-diabetic rats resulted in a 52.9-percent decrease in blood glucose levels [84]. Similar results were obtained by Dandu and Inamdar with oral administration of an aqueous extract of Andrographis paniculata leaves. A dose of 400 mg/kg lowered blood glucose level of streptozotocin-induced animals and increased activity of superoxide dismutase and catalase. Oral administration of the decoction also significantly reduced blood glucose levels in alloxaninduced diabetic rats, and reduced food and water intake compared to vehicle-treated diabetic controls [85].

Andrographolide dose-dependently reduce plasma glucose concentration in streptozotocin-induced diabetic rats and normal rats, with a more marked effect in normal rats than on diabetic rats. Andrographolide also attenuates the increase in plasma glucose in response to an intravenous 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, which indicates that the glucose lowering effect of andrographolide could be due to better glucose utilization by skeletal muscle [86]. However, after in vitro experiments, Wibudi and his coworkers concluded 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 [87]. Antidiabetic effect of A. paniculata was also studied by several other researchers thus proving its effect against diabetes [88-90].

Anti-diarrhoeal and intestinal effects

Diarrhoeal diseases are one of the top ten causes of death worldwide, especially for children under the age of five in developing countries [91]. An inflammation of the intestinal tract can cause acute diarrhoea. The inflammation can be caused by pathogenic bacteria overgrowth 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 over use 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 [92]. An inexpensive and easily obtainable herbal remedy would benefit many people, especially those in developing countries. Experiments in animals demonstrate that Andrographis paniculata can prevent diarrhoea. Extracts of A. paniculata have effectively shown activity against the diarrhoea connected with E. coli infections [93]. The A. paniculata components, Andrographolide and neoandrographolide showed comparable activity to loperamide (Imodium), the most common anti-diarrhoea drug. Gupta et al. reported that the active ingredients against diarrhoea are Andrographolide and deoxyandrographolide [94]. In Thailand, an extract made by boiling A. paniculata stem with methanol was reported to be effective against Proteus vulgaris and blended powder of stem and leaves can be effective against the Shigella bacteria but is not effective against cholera [95]. In a experiment conducted in a pharmacological research institute in Shanghai, China, 165 patients were given A. paniculata tablets equal to the amount of 15.6 g crude powder per day. Twenty-eight patients were given Fluroxone, a common drug used to treat dysentery. The result showed the effective rate of A. paniculata was 75.2% and the effective rate of Fluroxone was 71.4% [96]. A. paniculata was believed to be effective against bacterial dysentery and diarrhoea because it has antibacterial activities. Pleumjai and Sithisomwonges found that A. paniculata extracts with 70% and 80% ethanol could kill bacteria that cause diarrhoea such as E. coli and V. cholera [97], but Sindermsuk could not confirm this effect [92]. So it is necessary to extend these investigations using a broader spectrum of microbial pathogens of relevance to human health. 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 [98]. The

researchers compared the effect of Andrographolide and *A. paniculata* extract on intestinal brush-border membrane-bound hydrolases and suggested that both the extracts activated intestinal disaccharidases; the latter accelerated intestinal digestion and absorption of carbohydrate.

Anticancer activity

Cancer is a dreadful disease caused by abnormal and uncontrolled cell division. About 6 million new incidences of cancer are reported yearly worldwide. Nature has given man a variety of useful sources of remedies to cure a number of diseases. Natural products have played a significant role in drug discovery and development, especially agents active against cancer and infectious diseases [99]. More than 70 per cent of all cancer deaths occurred in low-and middle-income countries. The WHO noted that tobacco use, alcohol use, low fruit and vegetable intake, and chronic infections from hepatitis B virus (HBV), hepatitis C virus (HCV) and some types of human papillomavirus (HPV) are leading risk factors for cancer in low-and middle-income countries. Deaths from cancer worldwide are projected to continue rising with an estimated 12 million deaths by 2030 [100].

Tan et al. utilized the well-characterized epidermal growth factor receptor (EGFR) and transferrin receptor (TfR) expressed in epidermoid carcinoma (A-431) cells as a model to study the effect of andrographolide on receptor trafficking. Receptor distribution, the total number of receptors and surface receptors were analysed by immunofluorescence, Western blot as well as flow-cytometry respectively. Andrographolide treatment inhibited cell growth, down-regulated EGFRs on the cell surface and affected the degradation of EGFRs and TfRs. The EGFR was internalized into the cell at an increased rate, and accumulated in a compartment that co-localizes with the lysosomal-associated membrane protein in the late endosomes. This study sheds light on how andrographolide may affect receptor trafficking by inhibiting receptor movement from the late endosomes to lysosomes. The down-regulation of EGFR from the cell surface also indicates a new mechanism by which andrographolide may induce cancer cell death [101]. 14-DAG down-regulated the formation of death-inducing signalling complex, resulting in desensitization of hepatocytes to TNF-a-induced apoptosis. Pretreatment of hepatocytes with 14-DAG accentuated microsomal Ca-ATPase activity through induction of NO/cGMP pathway. This resulted in enhanced calcium influx into microsomal lumen with the formation of TNFRSF1A-ARTS-1- NUCB2 complex in cellular vesicles. It was followed by the release of full-length 55 kDa TNFRSF1A and a reduction in the number of cell surface TNFRSF1A, which eventually caused diminution of TNF-a signal in hepatocytes. The results demonstrate for the first time that 14-DAG desensitizes hepatocytes to TNF-a-mediated apoptosis through the release of TNFRSF1A. This can be used as a strategy against cytokine-mediated hepatocyte apoptosis in liver dysfunctions [102].

Microculture tetrazolium,3-(4,5-dimethylthiazol-2-yl)-2,5diphenyl tetrazolium bromide (MTT) and sulphorhodamine B (SRB) assays were utilized in assessing the in vitro growth inhibition and cytotoxicity of compounds by Jada and his coworkers. Flow cytometry was used to analyse the cell cycle distribution of control and treated cells. CDK1 and CDK4 levels were determined by western blotting. Apoptotic cell death was assessed by fluorescence microscopy and flow cytometry. Compounds, in nanomolar to micromolar concentrations, exhibited growth inhibition and cytotoxicity in MCF-7 (breast) and HCT-116 (colon) cancer cells. In the NCI screen, 3,19-(2-bromobenzylidene) andrographolide (SRJ09) and 3,19-(3-chloro-4-fluorobenzylidene) andrographolide (SRJ23) showed greater cytotoxic potency and selectivity than andrographolide. SRJ09 and SRJ23 induced G1 arrest and apoptosis in MCF-7 and HCT-116 cells, respectively. SRJ09 downregulated CDK4 but not CDK1 level in MCF-7 cells. Apoptosis induced by SRJ09 and SRJ23 in HCT-116 cells was confirmed by annexin V-FITC/PI flow cytometry analysis. The new benzylidene derivatives of andrographolide are potential anticancer agents. SRJ09 emerged as the lead compound in this study, exhibiting anticancer activity by downregulating CDK4 to promote a G1 phase cell cycle arrest, coupled with induction of apoptosis [103]. Kondo et al. reported that andrographolide (Andro), a major bioactive constituent of Andrographis paniculata, synergistically enhanced the inducible expression of CYP1A1 mRNA [104].

Chun and his coworkers reported that elevated interleukin-6 (IL-6), a major mediator of the inflammatory response, has been implicated in androgen receptor (AR) activation, cellular growth and differentiation, plays important roles in the development and progression of prostate cancer, and is a potential target in cancer therapy. Through drug screening using human prostate cancer cells expressing IL-6 autocrine loop, they found that andrographolide, a diterpenoid lactone isolated from a traditional Chinese and Indian medicinal plant Andrographis paniculata, could inhibit IL-6 expression and suppress IL-6-mediated signals. Andrographolide inhibits IL-6 expression at both mRNA and protein levels in a dose-dependent manner. Andrographolide suppresses both IL-6 autocrine loop- and paracrine loop-induced cell signaling including Stat 3 and Erk phosphorylation. Furthermore, andrographolide inhibits cell viability and induces apoptotic cell death in both androgen-stimulated and castration-resistant human prostate cancer cells without causing significant 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 [105].

In a study, conducted by Lin et al. Andrographis had been shown to inhibit non-small cell lung cancer (NSCLC) A549 cell migration and invasion via down-regulation of phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway. Here they demonstrated that Andrographolide inhibited the expression of hypoxia-inducible factor-1a (HIF-1a) in A549 cells. HIF-1a plays an important role in tumor growth, angiogenesis and lymph node metastasis of NSCLC. The Andrographolide induced decrease of cellular protein level of HIF- 1α was correlated with a rapid ubiquitin-dependent degradation of HIF-1a, and was accompanied by increased expressions of hydroxyl-HIF-1a and prolyl hydroxylase (PHD2), and a later decrease of vascular endothelial growth factor (VEGF) upon the treatment of Andrographolide. The VEGF expression appeared to be a consequence of HIF-1a inactivation, because its DNA binding activity was suppressed by Andrographolide. Molecular data showed that all these effects might be mediated via TGF\u00b31/ PHD2/HIF-1a pathway, as demonstrated by the transfection of TGF β 1 overexpression vector and PHD2 siRNA, and the usage of a pharmacological MG132 inhibitor. They also elucidated the involvement of Andrographolide in HIF-1a transduced VEGF expression in A549 cells and other NSCLC cell lines. These results highlighted the potential effects of Andrographolide, which may be developed as a chemotherapeutic or an antiangiogenesis agent for NSCLC in the future [106].

Petroleum ether and chloroform extracts were prepared from

the leaves of Andrographis paniculata and chromotographed over a column of silica gel, by gradient-elution technique and two compounds were isolated and purified by crystallization using methanol and ethyl acetate. The identified compounds were tested on different cancer cell lines such as HepG2 (hepato cellular), Hct-116 (Human colorectal) at various concentrations using MTT-Proliferation Assay and further confirmed by Dapi Staining and Acridine-Orange Staining techniques. Both the compounds have shown considerable activity at micro molar ranges [107].

Rajagopal et al. studied the cellular processes and targets modulated by andrographolide treatment in human cancer and immune cells. Andrographolide treatment inhibited the in vitro proliferation of different tumor cell lines, representing various types of cancers. The compound exerts direct anticancer activity on cancer cells 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 evidenced by increased proliferation of lymphocytes and production of interleukin-2. Andrographolide also enhanced the tumor necrosis factor-a 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 [108].

Das et al. investigated the protective role of Andrographis paniculata products (andrographolide and aqueous extract) on in vitro nicotine induced lymphocyte toxicity. Significant (P < 0.05) increase of superoxide anion generation, lipid peroxidation, protein oxidation and DNA fragmentation and decrease of cell viability, SOD and GSH content were observed in both 10 mM and 100 mM nicotine exposure. Different concentration of andrographolide and aqueous extract from *A. paniculata* supplement decreased oxidative stress in lymphocytes with the fall in superoxide anion generation, lipid peroxidation, protein oxidation, DNA fragmentation and rise in cell viability and the activities of the antioxidant enzymes; SOD and GSH. The findings indicated that *A. paniculata* products modulate the nicotine induced toxicity in lymphocytes through decreased superoxide mediated oxidative stress and DNA fragmentation. Hence, *A. paniculata* can be used as therapeutic means against nicotine mediated lymphocytes function [109].

Antimalarial activity

Malaria is one of the most widespread and vicious diseases affecting the mankind. The disease is caused by Plasmodium (Protozoa) of which four species P. falciparam, P.vivax, P. ovale and P. malariae are infectious to humans [110]. The disease is recognized as a wide spread epidemic in tropical and sub-tropical areas of the world, especially because of the remorseless rise in the resistance of P. falciparum to commonly used antimalarial drugs like chloroquine, mefloquine, mepacrine, pyrimethamine, primaquine and sulphadoxin [111,112]. Moreover, P. falciparum has acquired significant resistance and become prevalent in different parts of the world, which is a matter of serious concern [113,114]. Further, mefloquine resistance among P. falciparum has become more common in some of the eastern countries [115]. Even resistance against the novel drug-quinine has been recently reported from certain parts of South East Asia and Brazil [116]. The developing resistance towards conventional antimalarial agents has created serious threat for the treatment of malaria. Consequently, the attention has been focused on natural products and the search of an effective antimalarial agent. Chinese herbal drug artemether from Artemisia annua, is the out come of such efforts [117]. Andrographis paniculata, belonging to family Acanthaceae found mostly in tropical and subtropical regions of the world was used as bitter and remedy for malaria [118-120]. The active constituents of Andrographis paniculata are andrographolides and xanthones, which are isolated, characterized [41,121,122]. Andrographolide and 1,2-dihydroxy-6,8-dimethoxy-xanthone possess significantly higher activity in comparison of other isolated xanthones [118]. However, limited information is available for antimalarial activity of isolated xanthones. Hence, the objectives of the present investigation were the phytochemical screening of *A. paniculata* and evaluation of antimalarial activity of andrographolide and isolated xanthone, 5-hydroxy-7,8-dimethoxy flavone against P. berghei in vitro.

During last decade, several fundamental researches have been conducted to explore anti-malarial activity of many plants. In vitro studies of Dua and his coworkers revealed that compound 1,2-dihydroxy-6,8-dimethoxy-xanthone possessed substantial anti-plasmodial activity against Plasmodium falciparum with its IC50 value of 4 μ g 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 anti-malarial 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 [118]. Mishra et al. found that methanolic extract significantly inhibited Plasmodium falciparum at a 50-percent inhibitory concentration (IC50) of 7.2 μ g/mL [123].

In-vitro antimalarial activity of two active constituents of Andrographis paniculata was analyzed against Plasmodium berghei infection, propagated in Balb/c mice by injecting 1x105–1x107 parasitised red blood cells in citrate saline. Results indicated that chloroform soluble fraction of methanolic extract significantly (P < 0.05) inhibits parasitaemia (74 ± 3.8)% at 1 mg. mL⁻¹ in comparison to methanolic extract (54.9 ± 4.8)%, n-butanol (56.5 ± 2.8)% and ethyl acetate (47.8 ± 3.6)% soluble fractions of methanolic extract, respectively. However, it was also significantly (P < 0.05) different from chloroquine phosphate (82.6 ± 3.8)% inhibition at 0.39 mM. Moreover, andrographolide showed significantly (P < 0.05) better inhibition (53.9 ± 3.1)% against parasitaemia than 5-hydroxy-7,8-dimethoxyflavone (15.4 ± 2.9)%, but it was lower (P < 0.05) than that of chloroquine phosphate (61.5 ± 3.1 at 0.039 mM)% [124].

Upper respiratory infections

One of the most common causes of childhood illness and adult discomfort is upper respiratory infection. Upper respiratory infection includes any infection in the nose, throat, sinuses, and ears. The common cold is the most common upper respiratory infection. Viruses and bacteria in the surrounding environment may cause upper respiratory infection [125,126]. Crude aqueous or alcohol extractions of Andrographis paniculata and one principle, Andrographolide have been reported to be effective in the treatment of upper respiratory infections [96,127-131]. 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% AND) 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 catch

a 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 [130].

In a study conducted by Melchior et al. fifty adult patients received either 1020 mg extract or a placebo daily for 5 days to evaluate the efficacy of Andrographis paniculata extract on the initial symptoms of the common cold and uncomplicated sinusitis. The results demonstrated that the *A. paniculata* group took fewer sick leave days than the placebo group. Furthermore, 68% of treated patients felt totally recovered, but only 36% of the placebo group recovered [131].

In China, clinical studies of bacterial and viral respiratory infections demonstrated favourable effects after patients were orally taken A. paniculata or andrographolides. Investigations from the Sichuan Traditional Medicine Research Institution found that A. paniculata reduced body temperature in the treatment of infectious diseases associated with cold symptoms: 70 out of 84 treated patients achieved normal body temperature within 48 hours [131]. In 1972, researchers from the Chinese Herb Research Institute used deoxyandrographolide and neoandrographolide to treat 24 cases of upper respiratory tract infection, acute tonsillitis and bronchitis. The average recovery time was about 4 to 7 days compare to the placebo which was 14 days [96]. The antibiotic rifampin is usually used to treat tuberculosis. 10% of patients still die when rifampin is used alone [132]. In a study, an injectable solution of 2.5% andrographolide (50-80 mg/kg body weight per day) was used for two months. The therapeutic results were improved in seventy cases of tubercular meningitis. 30% of patients were cured with a fatality rate of 8.6%. The combination of Andrographolide plus rifampin resulted in a 2.6 fold decrease in fatality rates [133]. A. paniculata was used to treat cough and sore throat by Thamlikitkul et al. [127]. They compared A. paniculata leaf powder with Paracetamol and found that 6 g A. paniculata powder per day after 3 days reduced fever and sore throat better than Paracetamol. However, after 7 days there was no difference between them. In 1996, A. paniculata was compared with penicillin in its capacity to heal sore throat. The results showed that there was no significant difference in recovery rate between the two groups of patients. More than 75% of patients were cured with an additional 15% showing improvement [129].

More recently, *A. paniculata* extracts in fixed combination with Kan-jang, A. senticosus, Eleutherococcus senticosus Maxim, Schizandra chinensis Bail and Glycyrrhiza glabra L. extracts were also found to show significant improvement in the verum group as compared with the placebo in the treatment of uncomplicated upper respiratory tract infection[1,134-138].

Effect on inflammation and fever

Andrographis paniculata is used as a folk medicine for reducing inflammation. Three ingredients deoxyandrographolide, Andrographolide and neoandrographolide are effective in reducing inflammation [139]. In other studies it was found that Andrographis paniculata extracted with alcohol [140,141], *A. paniculata* extracted with water [140] and *A. paniculata* extracted with chloroform [141]reduced inflammation. Madav et al found that Andrographolide significantly inhibited carrageenin-, kaolin-and nystatin18 induced paw oedema (different models of inflammation) in rats after oral administration at doses of 30, 100 and 300 mg/kg bodyweight [142]. In China, it has been reported that Andrographolide has some beneficial effects as an anti-inflammatory agent [80,143], whereas Deng et al. who studied on rats and mice concluded that four lactones from *A. paniculata* have anti-inflammatory and anti-pyretic effects [19].

Deng et al. also suggested A. paniculata might exert its antiinflammatory effect through stimulation of the adrenal gland since the herb showed no effect when the adrenal gland of the animals were totally removed [19]. Habtemariam suggested that Andrographolide inhibited tumour necrosis factor-a to induce endothelial monocyte adhesion, which is part of the inflammatory process [144]. Other possible mechanisms involved in anti-inflammatory effects were also reported [145-148]. Shen et al. reported that the possible mechanism involved in its anti-inflammatory effect might be due to Andrographolide preventing oxygen radical production by human neutrophils [146]. Xia et al. and Hidalgo et al. 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 reducing the expression of proinflammatory proteins [147,148]. In a study from Thailand, rats were given injections with carrageenan (an agent for stimulating inflammation) to study the antiinflammatory effect of A. paniculata water extract ranging from 500, 1250, 2500 mg/body weight. The result showed that water extract of A. paniculata effectively reduced the paw volume in rats treated with A. paniculata whereas the control group did not [149].

The ability of *A. paniculata* to lower fever has been demonstrated in several laboratorios [149-151]. Rat studies have shown that fever produced by different fever-inducing agents, such as Pneumococcus spp., hemolytic Streptococcus, P. multocida and the chemical 2,4-dinitrophenol can be lowered by Andrographolide, neoandrographolide and dehydroandrographolide in China [150]. Indian researchers tested *A. paniculata* to determine whether it could reduce fever in rats. They found that there was a reduction in rectal body temperature for 30, 100 and 300 mg of Andrographolide /kg bodyweight. The antipyretic activity of 300 mg of Andrographolide/ kg bodyweight was comparable to that of 300 mg aspirin [146]. In Thailand, studies on rabbits showed that the antipyretic effect of 2.5 g 85% ethanol extract of A. paniculata/kg bodyweight was as effective as 300 mg/kg of aspirin [149].

Cardiovascular activity

Amroyan et al. 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 (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). They indicated that the mechanism of action may differ from that of nonsteroidal anti-inflammatory drugs. This mechanism is most likely combined with the cardiovascular and antithrombotic activity of *A. paniculata* [145].

Zhang and Tan found a hypotensive activity of aqueous extract of *A. paniculata* in rats and they suggested that the aqueous extract of *A. paniculata* lowers the systolic blood pressure of spontaneously hypertensive rats possibly by reducing circulating angiotensin converting enzyme in the plasma as well as by reducing free radical levels in the kidneys [25]. Hypotensive activity of Andrographolide in rats was also reported by Yu et al. [86].

Studies conducted by Zhang and Tanon on the cardiovascular activity of 14-deoxyandrographolide (DA) and 14-deoxy-11,12didehydroandrographolide (DDA) in rats, concluded that DA and DDA significantly decreased the mean arterial pressure and heart rate of anaesthetized rats. Both DA and DDA activated nitric oxide production

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in endothelial cells; the latter caused relaxation of the isolated rat thoracic aortae [152,153]. Chiou et al. reported that andrographolide inhibits nitrite synthesis by suppressing expression of inducible nitric oxide synthase (iNOS) protein in vitro, and the inhibition of iNOS synthesis may be good at haemodynamic effects of Andrographolide in endotoxic shock [154]. Zhao and Fang demonstrated that A. paniculata decreased the damage that occurred to the heart muscle when given to dogs that had one hour myocardial infection. Such damage occurs after the blood supply is restored to the muscle. A sudden influx of oxygen (which produces free radicals that damage tissue) and abnormally high amounts of calcium cause the damage [155]. In the same article, abnormal changes in heart were prevented by pretreatment with A. paniculata through electrocardiography. Clumping of platelets was also inhibited and clotting that could cause infarction was not induced [155]. The effect of A. paniculata was that it activated fibrionolysis, which dissolves clots in the body [150]. Hsu et al. reported that Andrographolide increased the radioactive glucose uptake in cultured myoblast cells and the uptake may reduce glucose in blood flow[156].

Hepatoprotective and choleretic activity

Andrographis paniculata has also shown to protect liver. In Ayurvedic medicine, there are 26 different formulations containing A. paniculata used to treat liver disorders. A. paniculata is hepatoprotective in mice treated with carbon tetrachloride or tert-butylhydroperoxide [157]. These chemicals are highly toxic compounds which damage the liver by causing lipid peroxidation [158]. They produced free radicals and the later destroyed cellular membranes around liver cells. Significant liver protection occurred when the A. paniculata compounds were given to animals three days earlier than when the toxic chemicals were given. This protection was assigned to the antioxidant ability of the A. paniculata compounds and the hepatoprotective effect could compare with the known hepatoprotective agent silymarin by biochemical parameter [159]. Handa and Sharma reported that Andrographolide was the major active antihepatotoxic principle of A. paniculata against carbontetrachloride [160]. A. paniculata was also reported to be better than silymarin in protecting the liver against paracetamol toxicity [161] and against paracetamol and galactosamine [162].

Hepatoprotective effect of Andrographolide was studied in rats. An acute hepatitis was induced by a single dose of galactosamine (800 mg/ kg, ip) and paracetamol (3 g/kg, po) in rats. The livers of experimental rats were used to monitor hepatoprotective activity by determining the serum transaminases (GOT and GPT), alkaline phosphatase and bilirubin in serum, hepatic triglycerides and histopathological changes [163]. The in vivo hepatoprotective effect of Andrographolide against galactosamine or paracetamol-induced hepatotoxicity in rats was confirmed by the results [161,162]. Infective hepatitis is an acute liver inflammation [164]. In India, twenty patients of infective hepatitis (hepatitis A) were treated with 200 mg of Andrographis paniculata extract twice times per day for over twenty-four days. The conjunctiva of the eyes and the urine changed colour from yellow to normal. It was reported that 80% of the patients were cured and 20% improved based on symptoms changes and biochemical tests. 90% of patients had regained appetites and 83% were relieved from general depression [165]. In another similar mode study in China, 83% of 112 cases of hepatitis were recovered [166]. Andrographolide showed choleretic activity in rat and guinea pig increasing bile volume as well as the amount of bile salts and bile acids [167]. The bile flow of the animals pretreated with Andrographolide was increased when paracetamol, which usually decreases bile production, was given to the animals. In this case, Andrographolide was more powerful as compared to silymarin. Andrographolide also increases the amount of bile that acetaminophen toxicity decreases [168].

Immunomodulatory activity

Intra-gastric administration of ethanol extracts of the stems and leaves (25 mg/kg bodyweight) or purified andrographolides (1 mg/kg bodyweight) to mice was reported to stimulate antibody production and the delayed-type hypersensitivity response to sheep red blood cells [169]. The extract and purified andrographolide was also reported to stimulate an innate immune response in mice, measured by macrophage migration index, phagocytosis of [14C] leucinelabelled E.coli, and proliferation of splenic lymphocytes stimulated with Andrographis paniculata extract [169]. However, the mechanism of the immunostimulation of andrographolide was not investigated. Andrographolide has been reported to have both immuno-stimulant and suppressant activities. The immunomodulatory property of a diterpene lactone andrographolide was reported to be associated with enhancement of proliferation of human peripheral blood lymphocytes as well as the production of key cytokines and the expression of immune activation markers (such as INF- γ , neopterin and β -2-microglobulin) in whole blood cells in culture in vitro [170]. Rajagopal et al and Kumar et al. reported the immunostimulatory activity of andrographolide in vitro in PHA stimulated HPBLs (human peripheral blood lymphocytes) by increased proliferation of lymphocytes and production of IL-2 [30,108].

However, Iruretagoyena et al. reported that andrographolide could interrupt T cell activation both in vitro and in vivo. This molecule could interrupt T cell proliferation and cytokine release in response to allogenic stimulation in vitro. T cell activation by antigen-pulsed dendritic cells (dendritic cells (DCs), one of antigenpresenting cells) was suppressed by andrographolide in B3Z/0T4H T cell hybridomas (DCs-T cell co-culture). The authors suggested that andrographolide could interrupt maturation of DCs and their ability to present antigens to T cells. In vivo immune responses such as antibody response to a thymus-dependent antigen (NP17-BSA) and delayedtype hypersensitivity were extremely lessened in mice treated with andrographolide [171]. In addition, Iruretagoyena et al. reported that andrographolide enhanced the tolergenic properties of immature DCs in Experimental Autoimmune Encephalomyelitis (EAE) by inhibiting NF-kappaB activation in murine DCs [172]. Andrographolide was also reported to reduce IFN-y and IL-2 production in murine T-cells stimulated with concanavaline A (Con A) in vitro [173]. Moreover, Qin et al. reported that andrographolide inhibited the production of TNF- α and IL-12 in macrophages stimulated by lipopolysaccharide. Hence, the molecular and cellular mechanisms responsible for the immunomodulatory properties of andrographolide are still unclear [174].

Anti-HIV activity

Researches conducted by Stephen and Comac 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 prove that andrographolide may inhibit HIV-induced cell cycle dysregulation leading to a rise in CD4 (+) lymphocyte levels in HIV-1 infected individuals [175].

Antiviral and Antifungal effects

Andrographolide, neoandrographolide 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 [176]. Fungal infections are one of the major health problems in tropical countries. Fungi or dermatophytes invade in to the keratinophilic region of the body and cause dermatophytosis. Radha et al. 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) [58]. Similar studies were conducted by Bobbarala et al. 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 [62].

Antifilarial, Antiprotozoal, and Antiplasmoidal activity

Andrographis paniculata extracts are also effective in killing filarial that obstructs lymph channels in the body, leading to gross swelling termed elephantiasis. The study was done in dogs. Since no toxic effects were apparent, researchers believed that the *A. paniculata* extract would be safe for humans. Water decoction of the leaves exhibited filaricidal activity, both in vitro and in dogs [139]. Xanthones isolated from the roots showed antiprotozoal activity against Trypanosoma brucei, Trypanosoma cruzi and Leishmania infantum [177]. The compound 1,2-dihydroxy-6,8-dimethoxy-xanthone possessed substantial antiplasmodial activity against Plasmodium falciparum with its IC 50 value of 4 μ gml-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 [118].

Nematicidal/Larvicidal/ Adulticial activity

Nematicidal efficiency of water and methanolic extracts of Andrographis paniculata were evaluated in vitro against rootknot nematode, Meloidogyne javanica and reniform nematode, Rotylenchulus reniformis by Goel et al. [178]. Observations on the larval/nematode mortality were recorded 48 h of their exposture to the extracts. Results revealed that methanolic extracts of Andrographis paniculata were highly effective at 1:5 concentration.

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 GI50 and FD 50 values of 100.4 and 159.7 μ g/g diet respectively. The ethyl acetate fraction possessed the highest oviposition-deterrent activity [179].

Larvicidal and ovicidal efficacy of benzene, hexane, ethyl acetate, methanol and chloroform extract of Andrographis paniculata was found to be more effective against Culex quinquefasciatus than Aedes aegypti.The LC50 values were 112.19, 137.48, 118.67, 102.05, 91.20 ppm and 119.58, 146.34, 124.24, 110.12, 99.54 ppm respectively. Among the five tested solvents, methanol and ethyl acetate crude extract was found to be most effective for ovicidal activity against two mosquito species. The extract of methanol and ethyl acetate exerted 100%mortality at 200 ppm against Culex quinquefasciatus and at 250 ppm against Aedes aegypti [180].

Safety and Contraindications

Andrographis paniculata has been perceived as safe in Traditional Chinese medicine. Although trial and error in humans may not be considered scientific, it is a way of determining wheather a substance is effective or harmful. When scientists began to investigate the safety of Andrographis paniculata, formal toxicological studies in animal models and human clinical trials confirmed that andrographolide and other compounds have very low toxicity. Burgos et al. 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 [181].

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. The other side effect as discussed above is antifertility. Overall, evidence to date indicates that andrographolides are naturally occurring compounds with low toxicity when used appropriately.

Conclusion

From the vast literature study and experimental results analysis it can be concluded that Andrographis paniculata is a traditional remedy for fever, cold and various infections. It also employs various immunological applications in cancer, immunomodulatory activity and viral diseases like HIV and others. The plant is also beneficial in treating cardiovascular disease and in preventing liver toxicity, thus improving functions of heart and liver. It also finds immense utility in abdominal problems, body aches, respiratory disorders, snake bites, allergic reactions, central nervous system and functioning of brain. Andrographis paniculata is reported to decrease fertility in animals and human beings. Taking great concern of the useful benefits of the plant, it can be advocated as a safe, highly important medicinal plant for mankind.

Conflict of Interest

The authors declare that they have no conflict of interest.

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