



Therapeutic potentials of Andrographolide from *Andrographis paniculata* : A review

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Abstract

Andrographolide, a bitter principle obtained from *Andrographis paniculata* (Family: Acanthaceae), is a diterpene lactone, responsible for various pharmacological activities. This is a well-known phytoconstituent from Indian System of Medicine, used in the management of different diseases since time immemorial. Research activities worldwide to exhibit the beneficial role of Andrographolide are continuously enriching the therapeutic arsenal of this important phytoconstituent. In addition to the well known pharmacological activities like hepatoprotective, antioxidant, hypoglycemic etc., recent advances in the management of immune system and neoplastic diseases make andrographolide the phytoconstituent of the hour. In this report an effort has been given to highlight the research findings related to therapeutic potentials and recent development in the pharmacological activities of andrographolide.

Keywords: Andrographolide, *Andrographis paniculata*, Therapeutic activity, Phytoconstituents.

1. Introduction

Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years. The plants and phytoconstituents in the traditional systems of medicine of many countries continue to play an essential role in healthcare. *Andrographis paniculata* Nees. (Family: Acanthaceae) is one such important plant, which has its traditional use in Ayurvedic (Indian), Thailand and Chinese medicine, owing to the geographical distribution

of the plant. Andrographolide is the active component obtained from the aerial parts of this plant, having very bitter taste. It is a bicyclic diterpenoid lactone (Fig.1) with multiple pharmacological activities. The traditional uses include treatment of fever, inflammation, common cold, upper respiratory tract infection, tonsillitis, pharyngitis, laryngitis, pneumonia, tuberculosis, pyelonephritis, hepatic impairment etc. [1-8].

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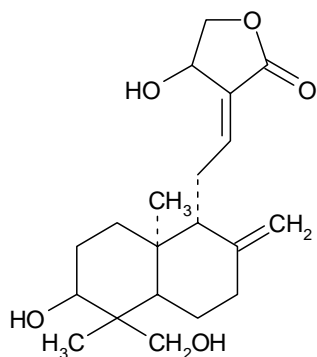


Fig. 1. Andrographolide

It also exerts antibiotic activity in some disease conditions [9]. Recent researches conducted to elicit newer therapeutic activities and the mode of action has lead to open a new avenue for potential future applications of this useful phytomolecule. An approach to sum up the therapeutic potentials of andrographolide was made in the light of traditional uses as well as evidence based research findings for providing a strong database for the future development in herbal drug research.

2. Role of Andrographolide in treatment of diseases

This review covers the beneficial roles of andrographolide in the management of diseases like hepatotoxicity, common cold, fever and inflammation, microbial diseases, diarrhea and intestinal disorders, cardiovascular diseases, respiratory system impairment, nervous disorders, cancer, HIV and other viral infections, leishmaniasis, hyperglycemia, allergic manifestation etc. The fertility effects and the cholorectic activity of andrographolide have also been discussed.

The pharmacological activities with possible mechanism of action have been given in table 1

and also extensively discussed inside the text to make an up-to-date review on the therapeutic perspectives of andrographolide. Due to the scarcity of journals that published plant based research work, some previous works related to pharmacological activities of andrographolide have been published in non-indexed and obscure journals and therefore may have been missed in this article as citation for the present article were mostly taken from the Medline database.

2.1. Hepatoprotective activity

In Indian System of Medicine (Ayurveda), about 26 different polyherbal formulations containing *Andrographis paniculata* are mentioned as a popular remedy for the treatment of various liver disorders and an adequate number of pharmacological investigations have substantiated the therapeutic potential of andrographolide, principal chemical constituent of *A. paniculata* as a hepatoprotective agent. Andrographolide showed a significant dose dependent protective activity against paracetamol-induced toxicity on *ex vivo* preparation of isolated rat hepatocytes [8].

It exhibits protective effects on hepatotoxicity induced in mice by carbon tetrachloride or tert-butyl hydroperoxide (t-BHP) intoxication [6,10]. A study by Rana and Avadhoot (1991) showed that intragastric administration of alcoholic leaf-extract of *Andrographis paniculata* (300 mg/kg body weight/day, for eight days) to carbon tetrachloride intoxicated rats resulted in significant amelioration of affected liver. The extract effectively reduced the elevated enzyme level and normalized liver functions [11].

Andrographolide has also been shown to produce ameliorative effect in galactosamine induced acute hepatitis in rats [5] and prevents BHC induced increase in the activities of enzymes gamma-glutamyl transpeptidase, glutathione-S-transferase and lipid peroxidation [12].

Table 1.
Pharmacological activities of andrographolide

Sl. No	Pharmacological activities / Therapeutic effects	Possible mechanism of action	Ref.
1.	Hepatoprotective activity	Prevention of oxidation, inhibition of cytochrome P-450, stimulation of hepatic regeneration and inhibition of microsomal enzymes or lipid peroxidation	[6, 5, 11, 9]
2.	Protective effect against common cold	Stimulation of immune system	[3, 12]
3.	Antipyretic activity	Stimulation of immune system	[3, 12]
4.	Anti-inflammatory activity	Inhibits free radical production by modulation of protein kinase C (PKC)-dependent pathway and down-regulates up-expression of Mac-1, an essential integrin for neutrophil adhesion and transmigration	[18, 19]
5.	Antimicrobial activity	Antioxidant activity, particularly by reactivation of superoxide dismutase (SOD)	[24]
6.	Antidiarrhoeal activity	Due to antibacterial activity	[16]
7.	Cardiovascular activity	Activates fibrinolysis, increases blood clotting time, inhibits PAF-induced platelet aggregation and prevent induction of clot. Hypotensive effect possibly by reducing circulating angiotensin converting enzymes (ACE) in the plasma and by reducing free radical generation	[28, 26, 32, 33, 27, 29]
8.	Anti-hyperglycemic activity	Increases glucose utilization to lower plasma glucose in diabetic rats lacking insulin and inhibits oxidative stress.	[34, 35].
9.	Anti-fertility activity	Affects spermatogenesis	[40]
10.	Effects on nervous system	May act at the barbitol receptors in the brain	[14]
11.	Effects on respiratory System	Stimulation of immune system	[3, 12]
12.	Anti-Leishmanial activity	Antimicrobial activity and cytostatic and growth inhibitory activity against <i>L. donovani</i> amastigotes and reduces splenic parasitic burden	[51]
13.	Cholerectic Effect	Increases bile flow, bile salt and bile acids	[53]
14.	Anti-allergic activity	Mast cell stabilization	[65]
15.	Anticancer and immunomodulatory activity	Activation of antigen specific response and nonspecific immune response, down modulation of humoral and cellular adaptive immune responses, interference with T cell proliferation and cytokine release in response to allogenic stimulation.	[54, 60]
16.	Anti-HIV activity	Prevents transmission of virus to other cells, stops progress of disease by modifying cellular signal transduction, inhibits C-mos-kinase, involved in HIV propagation.	[62]

It is useful in the treatment of infective hepatitis, an acute inflammatory condition of the liver. It is also useful in the treatment of jaundice [13]. All the experimental models used to evaluate the hepatoprotective activity of andrographolide dealt with the chemicals responsible for damage of liver by causing lipid peroxidation, a process related to production of free radicals by the chemical attack lead to destruction of the cellular membrane that surrounded liver cells.

So the hepatoprotective effect provided by andrographolide was attributed to the anti-oxidant ability of the compound, which scavenges the free radicals generated during hepatotoxin challenge [6]. Apart from antioxidant activity, inhibition of cytochrome P-450, stimulation of hepatic regeneration [5, 14] and inhibition of microsomal enzymes or lipid peroxidation [10] could explain the hepatoprotective effect of andrographolide.

2.2 Prevention of common cold

Several clinical studies by researchers worldwide have proved the protective effect of andrographolide against common cold. It reduces the incidence and severity of common cold. In a controlled study, andrographolide was found to have a significant beneficial effect on tiredness, shivering, sore throat, muscular ache, rhinitis, sinus pains and overall disease [2, 4, 7]. The inhibitory activity of andrographolide against common cold may be due to its immunostimulant effect. As a preventive for common cold, studies showed that andrographolide may increase body's resistance to infection by stimulating the production of antibodies and large white blood cells that scavenge foreign matter [3, 15]

2.3. Antipyretic activity

According to Indian, Thai and Chinese traditional medicine, *Andrographis paniculata* dispels heat (i.e. antipyretic) and removes toxin, which makes it a good treatment for infectious

fever causing diseases. The ability of andrographolide to reduce fever has been demonstrated in several experiments. In rat studies, it has been shown that andrographolide can lower the fever produced by different fever-inducing agents, such as bacterial endotoxins, pneumococcus, hemolytic streptococcus, typhoid, paratyphoid and the chemical 2, 4-dinitrophenol [16]. It was found that andrographolide is as effective as the same dose of aspirin in reducing fever [17, 18].

2.4 Anti-inflammatory activity

The anti-inflammatory activity of andrographolide has been shown in many studies involving chemical induced inflammation. Aqueous extract of *Andrographis paniculata* in the dose of 20mg/100 g of body weight given orally to rats showed significant inhibition of carrageenin – induced paw oedema [19]. A study by Madav *et al.*, (1996) suggested that andrographolide produced a moderate anti-inflammatory activity in acute, sub-acute and chronic models of inflammation without adverse effects on gastric mucosa.

The results of the study showed that oral administration of andrographolide produced significant anti-inflammatory activity in different models of inflammation like Carrageenin, Kaolin, nystatin induced rat paw oedema, cotton pellet induced granuloma, adjuvant induced arthritis etc. [20]. Inflammation generated by histamine, dimethyl benzene, croton oil, and acute pneumocystis produced by adrenaline was significantly reduced by andrographolide treatment, suggesting that the anti-inflammatory effect seemed to work by a mechanism that involved the adrenal gland [21].

Recent reports have indicated that andrographolide has an anti-inflammatory effect by modulating macrophages and neutrophil activity. It significantly attenuated

lipopolysaccharide (LPS) induced microglial activation and production of reactive oxygen species, tumor necrosis factor- α (TNF- α), nitric oxide synthetase and cyclooxygenase-2 protein expression in BV-2 microglia in a dose dependent manner, as determined by Western blot analysis [22].

Further studies demonstrated that andrographolide prevents production of reactive oxygen species (ROS) by modulation of protein kinase C (PKC)-dependent pathway, thus down-regulates up-expression of Mac-1, an essential integrin for neutrophil adhesion and transmigration, the possible mechanism involved in its anti-inflammatory effect [23, 24]. Nitric oxide (NO) is a critical mediator in inflammation. It is continuously produced by the inducible isoform of NO Synthetase (iNOS) in inflammatory macrophages under stimulation of lipopolysaccharides (LPS) and some cytokines [25].

It was observed that andrographolide and neoandrographolide, obtained from *Andrographis paniculata* suppressed NO production, orally in a concentration dependant manner in activated macrophages *in vitro* and *ex vivo*, which account for the anti-inflammatory activity [26].

2.5. Antimicrobial activity

Andrographolide was shown to possess potent inhibitory activity against certain microbes, responsible for promoting some fatal diseases in human. Earlier report by Bhatnagar (1961) suggested that *Andrographis paniculata* has potent antibacterial, antifungal as well as antiviral activities [27]. The extracts of *Andrographis paniculata* were evaluated for antimalarial activity against *Plasmodium berghei*, one of the parasites that transmit malaria. The extracts were found to produce considerable inhibition of multiplication of the

parasites [28]. The molecule was found to produce significant antibacterial and antifungal activities against some bacteria and fungi [29].

A study in dogs showed the effectiveness of *A. paniculata* extract in killing filarial worms that obstructs lymph channels in the body, leading to gross swelling termed elephantiasis [30]. Alcoholic extract of *A. paniculata* showed good *in vitro* anthelmintic activity against human *Ascaris lumbricoides* [31]. The possible antimicrobial activity of andrographolide may be related to the antioxidant potential of the molecule, particularly due to reactivation of superoxide dismutase (SOD), a key antioxidant enzyme that protects the liver [32].

2.6. Antidiarrhoeal activity

A. paniculata extracts have been shown to have significant antidiarrhoeal activity in *E. coli* infected diarrhoea [33]. Andrographolide showed similar activity to loperamide, the most common antidiarrhoeal drug. In some clinical studies, andrographolide has been shown to produce significant inhibition of bacterial diarrhoea and dysentery in patients [21], which may be due to the antibacterial activity of the molecule.

2.7 Cardiovascular activity

Preliminary researches in animals have indicated that andrographolide can be useful in the treatment of coronary heart disease (CHD), particularly in preventing restenosis, a condition associated with CHD, which is characterized by closing of blood vessels or rapid return of atherosclerotic blockage following coronary angioplasty. Studies on rabbits given angioplasty showed that *A. paniculata* extract significantly prevented constriction or narrowing of blood vessels [34]. Andrographolide is also found to be useful in the management of myocardial infarction, characterized by presence of blood clots in the heart shortly after the beginning of symptoms.

Researchers have demonstrated that *A. paniculata* given to dogs one hour after development of myocardial infarction decreased the damage caused to heart muscle [35]. Extract of *A. paniculata* produced antihypertensive effect. Andrographolide inhibited the increase in blood pressure caused by nor-adrenaline [36].

It also exhibits dose dependent hypotensive effect on the systolic blood pressure of spontaneously hypertensive rats, possibly by reducing circulating angiotensin converting enzymes (ACE) in the plasma as well as by reducing free radical levels in the kidneys [37]. The hypotensive activity may also be due to its effect on alpha-adrenoceptors, autonomic ganglion and histaminergic receptors [38].

An experimental atherosclerotic rabbit model demonstrated the usefulness of andrographolide in atherosclerosis. The experiment showed the effect of the compound on nitric oxide, endothelin, cyclic guanosine monophosphate, lipid peroxide and superoxide dismutase and concluded that it possesses antioxidant activity in addition to preservation of endothelial function and maintenance of the balance of nitric oxide and endothelin [39].

The mechanism behind the cardiovascular activities of andrographolide seems to be largely related to its clot dissolving property. *A. paniculata* extract can increase blood clotting time and decreases the risk of subsequent restenosis, following angioplasty [34]. Andrographolide inhibited PAF-induced platelet aggregation and prevent induction of clot (thrombus) that could cause myocardial infarction [40, 41, 35].

Further research showed that the phytomolecule activates fibrinolysis, a natural process in the body that dissolves blood clots. It also relaxes the smooth muscle in the walls of blood vessels and has a blood pressure lowering effect [36].

2.8 Anti-hyperglycemic activity

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. A number of studies have shown that *A. paniculata* extract and the active metabolite andrographolide can exert potent anti-hyperglycemic as well as hypoglycemic activities. The anti-hyperglycemic action of andrographolide was investigated in streptozotocin induced diabetic rats.

Oral treatment of andrographolide decreased the plasma glucose concentration of streptozotocin –diabetic rats in a dose dependent manner. Similar treatment with andrographolide also decreased the plasma glucose in normal rats [42]. In several other studies to assess the hypoglycemic, antihyperglycemic and antidiabetic properties of both the extract as well as the isolated andrographolide have demonstrated that both of them possess potent anti-hyperglycemic activity responsible for their antidiabetic property [43-45]. The hypoglycemic property of andrographolide was related to the prevention of glucose absorption from gut caused by the molecule [45].

The mechanism of anti-hyperglycemic and antidiabetic activity of andrographolide was experienced by a study in isolated soleus muscle of streptozotocin-induced diabetic rats. Andrographolide enhanced the uptake of radioactive glucose and the mRNA as well as protein levels of subtype 4 form of the glucose transporter (GLUT4) in soleus muscle were increased, suggesting that andrographolide can increase the glucose utilization to lower plasma glucose in diabetic rats lacking insulin [42].

Its hypotriglyceridemic effect is also beneficial in the diabetic state [44]. Researchers have also indicated another mechanism behind the antidiabetic activity, which is related to its

inhibitory action against oxidative stress, a pathogenetic factor in the development of diabetic complications. It was found that *A. paniculata* extract showed significant antioxidant property in diabetic rats as evident from the status of different enzymes like super oxide dismutase, catalase, glutathione peroxidase etc. [43].

2.9 Anti-fertility activity

Andrographis paniculata and andrographolide have clear anti-fertility effects in experimental animals, both male and female. Several studies have been performed and reported to determine the actual effects on fertility. In one study, it was found that dry powder of the plant leaf stopped development and maturation of sperm cells (spermatogenesis) in male rats [46]. Another study by Zoha *et al* to determine its anti-fertility effect on female mice shown pronounced contraception of the experimental animals, treated with powder [47], which may be due to prevention of ovulation in female mice.

The possible mechanism of anti-fertility effect of andrographolide has been demonstrated in a study by Akbarsha and Murugaian [48]. The compound was administered to 3 months old male Wister albino rats at two dose levels for 48 days. Fertility tests, analysis of the counts, motility and abnormalities of the cauda epididymidal spermatozoa, and histopathological-evaluation of the testis were carried out. The results showed a decrease in sperm counts along with several abnormal spermatozoa.

There was disruption in seminiferous epithelium and seminiferous tubules but Leydig cells appeared intact. It is inferred that andrographolide could affect spermatogenesis by preventing cytokinesis of the dividing spermatogenic cell lines. Sertoli cell damage and spermatotoxic effects are also apparent. Thus the study indicated toxic effect of the compound on

male reproductive system and possible protective use of andrographolide in male contraception. Several other studies have also been performed with the extract to determine the testicular toxicity and the effect on progesterone level in pregnant rats [49, 50].

The studies showed that the extract has no testicular toxicity in male rats and it doesn't cause significant reduction of progesterone concentration in pregnant rats.

2.10 Effects on nervous system

Psychopharmacological studies have been performed with *A. paniculata* extract to elicit its effect on nervous system. The extract exhibited a significant alteration in behaviour pattern and a reduction in spontaneous motility. It also prolonged pentobarbitone-induced sleeping time in experimental animals [51]. As per the reported data, andrographolide can penetrate the blood brain barrier and concentrates in the brain, particularly in the spinal cord [52].

Several other studies have shown that *A. paniculata* products have a sedative effect. It has an additive effect to barbital as anesthesia when given to mice. The products have a quick onset and longer duration of anesthetic activity. The studies indicated that *A. paniculata* products might act at the barbital receptors in the brain [17].

2.11. Effects on respiratory system

Current evidences suggested that *Andrographis paniculata* extract alone or in combination can be an appropriate alternative treatment of uncomplicated acute upper respiratory tract infections [53, 54]. Andrographolide has been used to treat upper respiratory tract infections in the traditional system of medicine. It is effective against tonsillitis and tuberculosis. In one study, *A. paniculata* was used to treat 129 cases of acute tonsillitis [55].

In another study on tubercular meningitis, andrographolide injection in combination with rifampicin cured the patients with a 2.6 fold decrease in fatality rates [56]. In a double blind placebo-controlled study of *A. paniculata* fixed combination Kan Jang in the treatment of acute upper respiratory tract infection including sinusitis, it was observed that the combination had an inhibiting effect against respiratory tract infection and it relieved the inflammatory symptoms of sinusitis [57].

Two randomized double – blind, placebo controlled parallel clinical trials involving 46 patients for the pilot study and 179 patients for the phase III study were performed to evaluate the effect of standardized *Andrographis paniculata* Herba Nees extract fixed combination (Kan Jang) in uncomplicated upper respiratory tract infection. The results of both the studies showed improvement in muscle soreness, sore throat, dryness in throat, cough frequency as well as production and body temperature in the *Andrographis paniculata* treated groups.

Thus the study indicated that *Andrographis paniculata* fixed combination reduced the common symptoms of uncomplicated upper respiratory tract infection [58]. The uncontrolled Chinese clinical studies, showed that both bacterial and viral respiratory infections were treated effectively with andrographolide and *A. paniculata*. In a randomized and double blind trial involving 152 patients with pharyngotonsillitis (inflammation of the pharynx and tonsils), higher dose of andrographis (6 g / day) is found to be as effective as paracetamol for treating fever and sore throat, whereas lower dose of the plant extract (3 g / day) produced less significant effect [59].

The mode of action in treating respiratory tract infections may be due to immunostimulatory and

anti-inflammatory activities of andrographolide, which also accounted for the preventive effect of the molecule in common cold.

2.12 Anti-leishmanial activity

Andrographolide has proven therapeutic activity in leishmaniasis. The anti-leishmanial activity of the molecule was tested *in vivo* against experimental leishmaniasis in hamsters. It was observed that andrographolide in different delivery systems exhibited a dose dependent reduction of parasitic burden of spleen of hamsters [60]. The anti-leishmanial activity of andrographolide may be due to its antimicrobial property.

The presence of lactone group in andrographolide, as in polyene antibiotics, may further increase the microbicidal property of the compound. In addition, andrographolide showed potent growth inhibitory activity [61] against M1 tumor cell-line proving its cytostatic activity. Andrographolide and its derivative may have similar cytostatic and growth inhibitory activity against *Leishmania donovani* amastigotes, causing a reduction in splenic parasitic burden [60].

2.13 Cholorectic effect

Intraperitoneal administration of andrographolide to male albino rats of H. M. strain at a dose of 20, 40 and 80 mg /kg body weight significantly enhanced the rate of bile flow in a dose dependant manner. It also stimulated the aqueous secretion into the bile in addition to an enhancement in the solid residue and bile salts in bile. The enhancement in the rate of bile flow excretion along with the increase in the solid residue of bile indicated the cholorectic property of this molecule [62].

It also produced a dose dependent cholorectic effect in conscious rats and anaesthetized guineapigs by increasing bile flow, bile salt and

bile acids. The paracetamol induced decrease in volume and contents of bile was prevented significantly by andrographolide pretreatment [63].

2.14 Anti-allergic activity

Andrographis paniculata is widely used in Indian system of medicine for the treatment of different type of diseases including allergic manifestations as well as complications related to skin. Earlier studies have supported its use in the treatment of dermatological diseases [64].

A study by Gupta *et al.*, (1998) revealed the anti-allergic activity of andrographolide and neoandrographolide, active constituents of *Andrographis paniculata*. The molecules were tested for anti-passive cutaneous anaphylaxis (PCA) and mast cell stabilizing activities in rats. It was observed that both andrographolide and neoandrographolide significantly inhibited PCA in a dose dependant manner. They also significantly protected mast cell degranulation induced by compound 48/80 or egg albumin. The mechanism behind the anti-allergic activity of andrographolide seemed to be due to its mast cell stabilizing property [65].

2.15 Anticancer and immunomodulatory activity

Andrographolide and *A. paniculata* extract was shown to be impressive in the treatment of cancer in different experiments. Studies on mice showed that it is a potent stimulator of the immune system. *A. paniculata* and andrographolide worked in two ways. These are (1) Activation of antigen specific response that involves antibodies, which are made to counteract the invading microbes and (2) Activation of nonspecific immune response, which deals with destruction of invaders by macrophage cells.

Activation of both the responses by *A. paniculata* makes it effective against various infections as

well as cancer. Ethanolic extract of *Andrographis paniculata* as well as andrographolide and neoandrographolide were investigated for their immunostimulatory activity in experimental animals and it was observed that *Andrographis paniculata* is a potent immunostimulant and enhanced both antigen specific and non specific responses.

The extract induced about a three-fold increase in the Hemagglutinating Antibody (HA) titer and a more than two-fold increase in the Hemolytic Plaque Forming Cells (PFC) assay in the treated animals in comparison to the controls. The Delayed Type Hypersensitivity (DTH) response to Sheep Red Blood Cells (SRBC) also increased. Andrographolide as well as neoandrographolide also enhanced these parameters, which indicated the immunostimulatory activity of the molecules. [66].

Both andrographolide and *A. paniculata* ethanolic extract induced significant stimulation of antibody and delayed type hypersensitivity (DTH) response to sheep red blood cells in mice. These also stimulated nonspecific immune response of the animals measured in terms of macrophage migration index (MMI), phagocytosis of ¹⁴C-leucine labeled *E. coli* and proliferation of splenic lymphocytes.

A study on mouse myeloid leukemia (M1) cells showed potent cell differentiation inducing activity of the methanol extract of *A. paniculata* as well as the diterpenoid lactone towards M1 cells [61]. Beside cell differentiation, andrographolide also showed cytotoxic effect against cancer cells. The cytotoxic activity was demonstrated by Talukdar and Banerjee [67] against human epidermoid carcinoma (squamous cell carcinoma) of the skin lining of the nasopharynx and lymphocytic leukemia cells.

Work by Ajaya Kumar *et al.* exhibited potent anticancer and immunomodulatory activity of

andrographolide on diverse cancer cells, representing different types of human cancer and immune cells [68].

Several other studies by the researchers have proved its potent anticancer activity in various types of cancer like KB (human epidermoid carcinoma), P388 (lymphocytic leukemia) etc [69]. Panossian *et al* investigated the effect of both andrographolide and *A. paniculata* fixed combination Kan Jang on spontaneous and mitogen induced proliferation of human peripheral blood lymphocytes (HPBL), production of cytokines, immune activation markers and soluble receptors of interleukin-2 in whole blood cultures.

It was found that both exhibited activation and proliferation of immune competent cells *in vitro* on HPBL and stimulated the production of key cytokines and immune activation markers like INF-gamma, TNF- α , and neopterin [70]. One important study, dealing with the cellular processes and targets modulated by andrographolide in human cancer and immune cells explained the mechanism of action of andrographolide, pertaining to its anticancer and immunomodulatory activity.

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). The immunostimulatory activity of the molecule is represented by increased proliferation of lymphocytes and production of interleukin-2.

It also increased TNF- α production and CD marker expression, which account for its indirect anticancer activity [71]. Further, the molecular and cellular bases for immunomodulatory effect

of andrographolide was demonstrated by Iruretagoyeur *et al* in a mouse model of experimental autoimmune encephalomyelitis which showed that the molecule can down modulate both humoral and cellular adaptive immune responses and also interferes with T cell proliferation and cytokine release in response to allogenic stimulation [72].

2.16 Anti-HIV activity

Recent researches have indicated that *A. paniculata* as well as its active metabolite andrographolide have great promise for the treatment of viral infections related to HIV. Andrographolide prevented transmission of the virus to other cells and stopped the progress of the disease by modifying cellular signal transduction. Andrographolide probably does this by interfering with key enzymes (Cyclin dependent kinase CDK) responsible for transfer of phosphates, which helps in viral reproduction [73].

The phytoconstituent can also inhibit toxic effects of HIV on cells by inhibition of C-mos-kinase, an enzyme responsible for expression of C-mos, a genetic component involved in HIV propagation and T cell death. A phase I dose escalating clinical trial of andrographolide involving HIV positive patients and normal volunteers showed that andrographolide may inhibit HIV induced cell cycle deregulation, leading to arise in CD4 (+) lymphocyte levels in HIV-I infected individuals [74].

3. Conclusion

A recent trend of using traditional approaches to treat diseases has been revived all over the world and the efforts have resulted in new findings, showing immense potential of medicinal plants used in traditional systems. Andrographolide, a well-known phytoconstituent isolated from *Andrographis paniculata*, is used as a traditional

remedy for a vast array of diseases. Research activities and controlled clinical studies have proved its beneficial effects in reducing the prevalence and intensity of many life threatening systemic disorders in human.

It is also recognized as a safe biomolecule, which is evident from toxicological studies in animal model [75]. Exploration of the therapeutic potential of the phytoconstituents so much so their pharmacodynamic studies are major concern nowadays for drug development from natural resources [76]. These aspects should be explored to a much extent for Indian phytoceuticals, particularly to a great extent so as to establish the pharmacokinetics and dynamics data of these phyto-molecules being used in different diseases.

Therefore it is worthy to explore the therapeutic potentials of andrographolide based on its clinical implications. Several approaches for value added dosage form development of this potent molecule is under way at our laboratory to exploit the clinical use and pharmacodynamic potentials of this phyto-molecule in combating various diseases.

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