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Indigenous king of bitter (*Andrographis paniculata):* A review

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Abstract
Andrographis paniculata (King of bitters), commonly known as Kalmegh is belongs to the family of Acanthaceae. The objective of this study is to review the literature of Andrographis paniculata specifically articles pertaining to therapeutic benefits, chemical properties and pharmacological evaluation. It is extensively used in indigenous system of medicines as home remedy for various diseases in Bangladeshi traditional system. It is used to treat hepatitis, gastrointestinal tract and upper respiratory infections, fever, herpes, and a variety of other chronic and infectious diseases. *Andrographis paniculata* possess hepatoprotective, anti-inflammatory, immunostimulatory, antipyretic, antioxidant, hypotensive, antibacterial activities. Andrographis paniculata contains steroids, phenols, terpenoids, alkaloids, saponins, flavonoids were the active compounds present in the plant. The medicinal value of this plant is due to the presence of active ingredients viz andrographolide and neoandrographolide which are derivatives of diterpenoids.

Keywords: *Andrographis paniculata*, kalmegh, andrographolide**,** king of bitters

Introduction
Andrographis paniculata is an annual and branched plant with lanceolate green leaves and attains heights of 60-70 cm [1]. 2. It grows abundantly in Asian countries like India, Sri Lanka, Pakistan, Java, Malaysia and Indonesia. In India it is commonly known as Kalmegh mainly found in the plains of the country and is one of the commonly used medicinal plants in Ayurvedic and Unani systems of medicines. The plant is also known as the 'king of bitters' [2-3] because it is extremely bitter in taste in every part of plant body. On the basis of literature survey it has been observed that the aerial parts (leaves and stems) of the plants are most commonly used to extract the active phytochemicals, however the whole plant or roots are mentioned to a limited extend [3]. A. paniculata has a broad spectrum of pharmacological effects and some of them are extremely beneficial such as Hepatoprotective, antimicrobial, antifungal, antioxidant, anti-inflammatory, antipyretic, anticancer and antidiarrhoeal effects. According to Unani system of medicine it is useful in the treatment of chronic hepatitis.

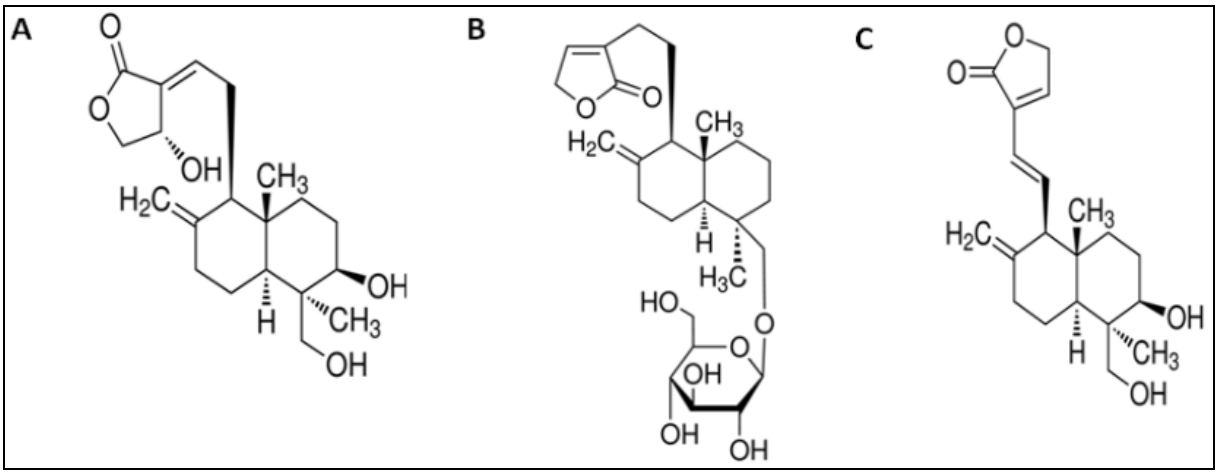
Vernacular names
Arabic: Quasabhuva, Assamese: Kalmegh, Azerbaijani: Acılar Şahı, Acılar Xanı (khanı) Bengali: Kalmegh, Chinese: Chuan Xin Lian, English: The Creat, King of Bitters, French: Chirette verte, Hindi: Kirayat, Kalpanath, Japanese: Senshinren.

Fig 1: *Andrographis paniculata*

Phytochemical constituents

A review of the literature reveals that the presence of various chemical constituents in the aerial parts of the Andrographis paniculata are andrographolide, which is diterpene lactone, colourless, crystalline, bitter in taste [4]. Other compounds include 14-deoxy-11-oxoandrographolide, didehydro andrographolide/andrographlide D, 14deoxyandrographolide, non-bitter compound is neo andrographolide, homoandrographolide, andrographosterin, andrograpanin, α-sitosterol, stigmasterol. Apigenin-7, 4-dio-methyl ether, 5-hydroxy 7,8,2, 3-tetramethoxy flavones, monohydroxy trimethyl flavones, andrographin, dihydroxy di-methoxy flavoue, panicolin, andrographoneo, andrographoside, andropani-culoside A(3,7,8) andrograpanin, Isoandrographolide and skollcaflavone (912). Six entlabdane diterpenoids i.e. 3-o-beta-Dglucopyranosyl-14, 19-dideoxyandrographolide, 14-deox, 17-hydroxyandrographolide, 19-o-[beta-D-apiofuranosy 1-2beta-D-glucopyranoyl]-3, 14-dideoxyandiographolide, 3-obeta-D-glucopyranosyl-andro-grapholide, 12S-hydroxy andrographolide and andrographatoside. These compounds showed inhibitor activity against several fungal and bacterial strains.

Dua *et al*. reported four xanthones 1,8-dihydroxy3,7-dimethoxy xanthone, 4,8-di-hydroxy-2, 7-dimethoxyxanthones, 1,2-dihydroxy-6, 8-dimethoxyxanthone and 3,7,8-trimethoxy-1-hydroxyxanthone from the roots [5].



Andrographolide Neoandrographolide 14-Deoxy-11,12didehydroandrographolide

Fig 2: Phytochemical constituents

Pharmacological activity

Hepatoprotective activity

Very few studies on the effects of crude extracts of A. paniculata on liver function are available. Most studies for hepatic effects have been conducted on either andrographolide or other purportedly active principles. Shukla *et al* reported significant choleretic effects of andrographolide in conscious rats and anesthetized guinea pigs. The protection of andrographolide against acetaminophen-induced reduction in volume and contents of bile was better than that produced by silymarin [6]. Multiple-dose pretreatment with arabinogalactan proteins and andrographolide was protective against ethanol induced hepatotoxicity in mice and was deemed comparable to the efficacy of silymarin [7]. Choudhury and Poddar reported that oral pre- and post-treatment of adult rats with an extract of A. paniculata was protective against ethanol-induced increase in serum transaminases. Administration of the extract to normal adult rats in single and multiple doses for seven and 15 consecutive days did not significantly effect serum transaminases [8]. A comparative study on the effect of leaf extract or andrographolide on carbon tetrachloride (CCl_4)-induced hepatic microsomal lipid peroxidation revealed a protective effect of a single oral dose of the extract and of andrographolide. However, high concentration CCl_4-induced microsomal lipid peroxidation in vitro was completely protected by the extract but not by andrographolide, indicating that the hepatoprotective effect is not solely due to the presence of andrographolide [9]. Hepatoprotective effects of the crude alcohol extract of leaves against CCl_4-induced liver damage have also been reported by Rana and Avadhoot [10].

A. Handa and Sharma compared andrographolide, methanol extract of the whole plant containing equivalent amounts of andrographolide, and an andrographolide-free methanol extract against CCl_4-induced liver damage in rats. The CCl_4-induced increases in serum transaminases, serum alkaline phosphatase, serum bilirubin, and hepatic triglycerides were inhibited by 48.6-, 32- and 15 percent, for andrographolide, methanol extract, and andrographolide-free methanol extract, respectively. Since all three treatments resulted in improvement in liver histology [11], a hepatoprotective role of A. paniculata constituents other than andrographolide is suggested and corroborates the observation made by Choudhury and Poddar [9]. The CCl_4-induced increase in pentobarbitone induced sleep time in mice is also completely normalized by andrographolide. The effects of intraperitoneal (i.p.) pretreatment for three consecutive days with andrographolide on CCl_4- or tert-butyl hydroperoxide-induced hepatotoxicity in mice were compared with two other diterpenes – andrographiside and neoandrographolide. Both compounds showed a greater protective effect than andrographolide. The protection by andrographiside and neoandrographolide was comparable to silymarin, and neoandrographolide normalized glutathione levels [12]. Trivedi *et al* observed protection by both the crude extract of A. paniculata and andrographolide against reduced activities of hepatic antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase), depletion of hepatic glutathione, and increased activities of hepatic γ-glutamyl transpeptidase, glutathione-S-transferase, and lipid peroxidase caused by

hexachlorocyclohexane in mice [13]. Oral or i.p. pretreatment with andrographolide was also protective against galactosamine-induced liver damage in rats and prevented changes in biochemical parameters and liver histology. Similar protection was observed when rats were treated with andrographolide post-acetaminophen challenge, [14] and on an ex vivo preparation of isolated rat hepatocytes [15]. Various extracts and constituents of A. paniculata were used in the experiments mentioned in this subsection. All showed hepatoprotective effects. A. paniculata also showed benefits against liver damage caused by agents with different hepatotoxic mechanisms, suggesting A. paniculata and its constituents are not agent-specific and might have broad-spectrum hepatoprotective effects. More research is needed to establish the identity of the most effective component(s) for hepatoprotection. Large, multicenter, clinical studies are warranted to determine whether A. paniculata is efficacious in patients with liver diseases of various origins.

Immunostimulatory activity

Intragastric administration of an ethanol extract of the aerial parts (25mg/kg body weight) or purified andrographolides (1 mg/kg body weight) to mice stimulated antibody production and the delayed-type hypersensitivity response to sheep red blood cells [16]. The extract also stimulated a non-specific immune response in mice, measured by macrophage migration index, phagocytosis of [14C] leucine-labelled E. coli, and proliferation of splenic lymphocytes [17]. The extract was more effective than either andrographolide or neoandrographolide alone, suggesting that other constituents may be involved in the immunostimulant response [18].

Antipyretic activity

Intragastric administration of an ethanol extract of the aerial parts (500mg/kg body weight) to rats decreased yeast-induced pyrexia [19]. 11. The extract was reported to be as effective as 200 mg/kg body weight of aspirin, and no toxicity was observed at doses up to 600 mg/kg body weight [20]. Intragastric administration of andrographolide (100 mg/kg body weight) to mice decreased brewer's yeast-induced pyrexia [21]. Intragastric administration of deoxyandrographolide, andrographolide, neoandrographolide or 11, 12-didehydro- 14-deoxyandrographolide (100 mg/kg body weight) to mice, rats or rabbits reduced pyrexia induced by 2, 4-dinitrophenol or endotoxins [22].

Antioxidant effects

Verma and Vinayak [23] related the antioxidant effects of the aqueous extract on liver defense systems in lymphoma bearing mice. The aqueous extract and hydro alcoholic extract of the medicinal plant A. paniculata showed the increase in activities such as catalase, superoxide dismutase and glutathione-Stransferase enzymes and reduced lactate dehydrogenase activity. The results performed with that of aqueous extract of A. paniculata exhibited a greater antioxidant activity than the ethanol extract in all model systems tested. The function of Hydroalcoholic extract of A. paniculata possesses oxidative alterations in myocardium and confers substantial cardioprotective activity by facilitating in retaining the cardiac function in a norma manner [24].

Hypotensive activity

Andrographis paniculata is reported to have, by acting through β- adrenoceptors, autonomic ganglion receptor andangiotensin converting enzyme (ACE) inhibitory activity [25]. 103. The 4th week of the extract treatment in SH rats significantly increases the relaxation responses to ACh as a result of possible improvement in the endothelial function; these are comparable with the study. Conversely the plant possesses a remarkable capability to challenge the nor-epinephrine induced contractions resulting in vaso relaxation in isolated rat [26]. 104. The improvement in relaxation responses to ACh following chronic administration of chloroform extract is most likely due to the activation of NO synthesis and ultimate stimulation of NO production in endothelial cells. Moreover, the effects of chronic administration are evidently suggestive of increased responsiveness of the vascular smooth muscle to NO since 4-week treatment with the extract was found to enhance the relaxation responses to the action of the endothelium-independent vasodilator SNP. Endothelial protective effects of *Andrographis paniculata* chloroform extract were comparable to the effects of Verapamil, which acts by blocking the L-type Ca2+ current and high K+ activated pathways to relax the smooth muscle [27].

Antidiabetic activity

Antidiabetic property of A paniculata was confirmed by Borhanuddin *et al*. and Husen *et al*. in aqueous extract [28-29] and by Zhang *et al*. in ethanolic extract [30]. Along with antihyperglycaemic property, the ethanolic extract may also reduce oxidative stress in diabetic rats as studied by Zhang *et al*. [31]. Further, it was concluded by Yu BC *et al*. that the andrographolide was responsible for the antihyperglycemic activity [32]. Finally the antidiabetic potential of A. paniculata was found to restore impaired estrous cycle in alloxan induced diabetic rats [33].

Anti-inflammatory activity

A. paniculata can also inhibit the production of inflammatory mediators and alleviate acute hazards at its optimal dosages [34]. Shen *et al*. observed that the andrographolide, an active component of A. paniculata, inhibits inflammatory responses by rat Neutrophils [35]. It was also found to inhibit the tumor-specific angiogenesis by regulating the production of various pro and antiangiogenic factors byin vivo and in vitro studies [36]. In a study by Wang *et al*. [37] A. paniculata was found to alleviate atherosclerotic artery stenosis induced by deendothelialization and high cholesterol diet as well as lower restenosis rate after experimental angioplasty. Further in a research by Coon *et al*. [38] it was also found to be safe and efficacious for the relief of symptoms of uncomplicated upper respiratory tract infection.

Antibacterial activity

An ethanol extract of the leaves inhibited the growth in vitro of Escherichia coli and Staphylococcus aureus1. A 50% methanol extract of the leaves inhibited growth in vitro of Proteus vulgaris [39]. However, no in vitro antibacterial activity was observed when dried powder from the aerial parts was tested against E. coli, Staphylococcus aureus, Salmonella typhi or Shigella species [40].

Anti-plasmodial activity

In vitro studies of Dua and his coworkers (2004)146 revealed that compound 1,2-dihydroxy- 6,8-dimethoxyxanthone possessed substantial anti-plasmodial activity against Plasmodium falciparum with its IC50 value of 4 µg ml−1. Xanthones bearing hydroxyl group at 2 positions demonstrated most potent activity while xanthones with

hydroxyl group at 1, 4 or 8 position possessed very low activity. In vivo antimalarial sensitivity test of this compound on Swiss Albino mice with Plasmodium berghei infection using Peters' 4-day test gave substantial reduction (62%) in parasitaemia after treating the mice with 30 mg kg−1 dose84 The methanolic extract significantly inhibited Plasmodium falciparum at a 50-percent inhibitory concentration (IC50) of 7.2µg/mL[41].

Anticold activity

One clinical trial has investigated the efficacy of a standardized A. paniculata extract to prevent the common cold by Caceres 107 healthy students in a rural school had daily taken either placebo or a dose of 200 mg (minimum 5.8%) of Kan Jang (a formulation of A. paniculata provided by the Swedish Herbal Institute) for three months. The number of colds occurring over a three month period was observed. After 1 month no significant difference was found. However, the difference was statistically significant in the second and third month. The placebo group was 2.1 times more likely to catcha cold than the Kan Jang group. The incidence of the common cold was 30% in the A. paniculata group, whereas the incidence was 62% in the placebo group [42].

Cardiovascular effects

Aqueous extract of A. paniculata produced a dose-dependent fall in systolic blood pressure of both spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto rats, with a corresponding significantly decrease in plasma angiotensin converting enzyme (ACE) activity and lipid peroxidation in kidneys in extract-treated SHRs. The decreases in ACE activity and lipid peroxidation were not significantly altered in normotensive Wistar-Kyoto rats, an indication that suggests its hypotensive effect in hypertensive and normotensive rats is not mediated through identical mechanisms [43]. The hypotensive effect of n-butanol and aqueous fractions of the crude water extract is antagonized or attenuated by phentolamine, hexamethonium, pyrilamine, and cimetidine, but not by propranolol, atropine, or captopril [44]. However, the fall in mean arterial pressure produced by 14-deoxy-11, 12-didehydroandrographolide (DDA), one of the three active diterpenoids, in anesthetized Sprague-Dawley rats was attenuated in the presence of propranolol, hexamethonium, and captopril. DDA also antagonized the positive chronotropic effect of isoproterenol on the isolated rat right atria in a non-competitive and dose-dependent manner [45]. Hypotensive and negative chronotropic effects of DDA have been corroborated by a recent study that suggested that vascular smooth muscle is the major site of hypotensive activity of DDA and high-DDA extracts [46].

Antiviral activity

Andrographolide, neoandrographolide and 14-deoxy11, 12-didehydroandrographolide are reported to be viricidal against herpes simplex virus 1 (HSV-1) without having any significant cytotoxicity at viricidal concentrations [47].

Effects on reproductive systems

A number of animal studies report an effect of Andrographis paniculata on male and female reproduction. Early reports of oral administration of powdered stem indicated an antifertility effect in male Wistar mice, but no impact on fertility in female mice. In has also been reported that administration of Andrographis paniculata resulted in abortion in pregnant rabbits. Intraperitonially injection of the decoction of aerial parts to female albino mice was reported to prevent implantation and caused abortion at different gestation periods. Early pregnancy was also terminated by intramuscular, subcutaneous, and intravenous administration. Administration of progesterone or luteinizing hormone-releasing hormone completely or markedly antagonized the abortifacient effects, indicating an interference with progesterone activity as a potential mechanism for this abortifacient effect. In addition, the herb is reported to suppress growth of human placental chorionic trophoblastic cells in vitro. Zoha *et al* [48] fed female mice sun-dried Andrographis powder at a dose of 2 g/kg body weight/day for six weeks. When they were mated with untreated males of proven fertility, pregnancy was inhibited in 100 percent of the animals. Conversely, more than 95 percent of untreated female mice in the control group became pregnant when mated with males in a similar fashion. Akbarsha *et al* administered dry leaf powder to male albino rats (20 mg daily for 60 days) reported inhibition of spermatogenesis, degenerative changes in the seminiferous tubules, regression of Leydig cells, and regressive and/or degenerative changes in the epididymis, seminal vesicle, ventral prostate, and coagulating glands. Andrographolide also produced similar results when orally administered to male Wistar albino rats for 48 days. Sperm count and sperm motility were decreased and sperm abnormalities were noted. However, Burgos *et al* [49] found no testicular toxicity in male Sprague Dawley rats after treatment with a standardized dried extract in doses of up to 1,000 mg/kg daily for 60 days. Its analysis was based on testicular weight and histology, ultra structural analysis of Leydig cells, and testosterone levels. Extract of Andrographis paniculata also did not affect the progesterone levels in pregnant rats when administered orally in doses of 200, 600, and 2,000 mg/kg daily during the first 19 days of pregnancy. Burgos *et al* reported that dried extract of A. paniculata induces uterine relaxation by blocking voltage-sensitive calcium channels. A phase I clinical study on Kan-Jang (a combination of A. paniculata and Eleutherococcus senticosus) reported no significant negative effects on sperm quality and fertility of healthy adult males. Existing evidence is too inconsistent, with some findings directly contradicting others, to reach any definitive conclusion about the reproductive effects of *Andrographis paniculata*. "e existing evidence does suggest that A. paniculata is unlikely to be an effective form of birth control. Further studies on short- and long-term effects on fertility are warranted.

Immuno-modulatory activity

Andrographis paniculata has a wide range of medicinal and pharmacological applications. It was used in different traditional system of medicine and exhibits many activities. In 1993, Puri *et al*. reported that the ethanolic extract and purified diterpene andrographolides of A. paniculata (Acanthaceae) induced significant stimulation of antibody and delayed type hypersensitivity (DTH) response to sheep red blood cells (SRBC) in mice [50]. While in 2005, Reddy *et al*. isolated six known compounds andrographolide, 14-deoxy-11,12-didehydroandrographolide, andrograpanin, 14-deoxyandrographolide, (+/-)-5-hydroxy-7,8-dimethoxyflavanone, and 5-hydroxy- 7,8-dimethoxyflavone and one Novel bis-andrographolide from the aerial parts of A. paniculata and found positive results for the antiHIV and cytotoxic activity [51]. The immunomodulatory properties of a diterpene lactone andrographolide and a standardized

preparation (Coded name -Kan Jang) of A. paniculata were investigated. Proliferation of peripheral blood lymphocytes (PBL) induced by phytohemagglutinin (PHA) was enhanced by costimulation with Andrographolide and Kan Jang. At the same time Andrographolide and Kan Jang inhibit spontaneous proliferation of PBL in vitro [52].

Cytotoxic activity

Hydro-alcoholic extract of A. paniculata was examined by Singh RP *et al*. to indicate the chemopreventive potential of A. paniculata against chemotoxicity including carcinogenicity on drug metabolizing enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase (LDH), and lipid peroxidation in the liver of Swiss albino mice. In the lung, SOD, catalase and DTD, in the kidney catalase, DTD and GST, and in the fore stomach SOD and DTD showed a significant increase at both dose levels of treatment [53]. While the in vivo anticancer activity of the isolated compound Andrographolide is substantiated against B16F0 melanoma syngenic and HT-29 xenograft models, these results by Rajagopal *et al*. in 2003 suggest that andrographolide is an interesting pharmacophore with anticancer and immunomodulatory activities [54]. Further, in 2004, a positive anticancer and immunomodulatory activity of the methanolic extract were screened Kumar *et al*. for human cancer and immune cells [55]. In 2005 Cheung *et al*. carried out the in vitro cytotoxicities of the ethanolic extract of A. paniculata (APE) and its main diterpenoid components evaluated in various cancer cells. APE was found to be significantly growth inhibitory to human acute myeloid leukemic HL- 60 cells with an IC (50) value of 14.01 µg/ml after 24 hours of treatment [56]. In 2005, Wiart *et al*. found that some isolated compounds, i.e. Andrographolide, neoandrographolide, and 14-deoxy-11,12- didehydroandrographolide, ent-labdene diterpenes showed viricidal activity against herpes simplex virus 1 (HSV-1). None of these compounds exhibited significant cytotoxicity at viricidal concentrations [57]. Further, aqueous extracts of A. paniculata are expected to be scorpion venom antidotes with low cytotoxicity [58]. An early enhancement of antibody-dependent complement mediated cytotoxicity of A. paniculata was also observed by Sheeja *et al*. in 2007 in normal as well as tumor-bearing animals. APE and ANDLE administration could significantly enhance the mitogen-induced proliferation of splenocyte, thymocyte, and bone marrow cells. The production of interleukin-2 and interferon-gamma in normal and Ehrlich ascites carcinoma-bearing animals was elevated [59] latest by 2006 in an experimental study by Zhou *et al*., it was shown that the key mediators in relaying the cell death signaling initiated by Andrographolide was found to be proapoptotic Bcl-2 [60].

Antivenom activity

Intraperitoneal injection of an ethanol extract of the aerial parts (25 g/kg body weight) to mice poisoned with cobra venom markedly delayed the occurrence of respiratory failure and death17. The same extract induced contractions in guinea-pig ileum at concentrations of 2 mg/ml. The contractions were enhanced by physostigmine and blocked by atropine, but were unchanged by antihistamines17. These data suggest that extracts of the aerial parts do not modify the activity of the nicotinic receptors but produce significant muscarinic activity, which accounts for its antivenom effects [61].

Antimalarial activity

A 50% ethanol extract of the aerial parts inhibited the growth of Plasmodium berghei both in vitro (100 mg/ml) and in mice after intragastric administration (1 g/kg body weight) [62]. Intragastric administration of a 1-butanol, chloroform or ethanol–water extract of the aerial parts to Mastomys natalensis inhibited the growth of P. berghei at doses of 1–2 g/kg body weight. Andrographolide (5 mg/kg body weight) and neoandrographolide (2.5mg/kg body weight) were also effective when administered by gastric lavage [63].

Anti-human immunodeficiency virus (HIV) activity

Aqueous extracts of the leaves inhibited HIV-1 infection and replication in the lymphoid cell line MOLT-4[64]. A hot aqueous extract of the aerial parts reduced the percentage of HIV antigen-positive H9 cells [65]. Dehydro andrographolide inhibited HIV-1 and HIV-1 (UCD123) infection of H9 cells at 1.6mg/ ml and 50mg/ml, respectively, and also inhibited HIV-1 infection of human lymphocytes at 50mg/ml [66]. A methanol extract of the leaves suppressed syncytia formation in co-cultures of uninfected and HIV-1infected MOLT cells (median effective dose [ED50] 70mg/ml) [67].

Conclusions

Andrographis paniculata has been treating various diseases and which are highly showing preventative effects against ailments like liver damage, infection, hyperglycemia, cancer, etc. Andrographolide, is a diterpenoid lactone having a diversity of pharmacological effects specified in indigenous system of medicine. In addition to it a great number of pharmaceutical uses, of which andrographolide has some side effects like nausea, vomiting, loss of appetite which can only be seen upon overdosing. Therefore, researchers may further be undertaken to develop potent formulations consisting of *Andrographis paniculata* and its isolated molecule, andrographolide by making use of herbal drug delivery systems.

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