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A systematic comprehensive review on therapeutic potential of *Andrographis paniculata* (Burm. f.) Wall. ex Nees

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Abstract
Andrographis paniculata is the most predominantly used plant in the Indian traditional systems of Ayurveda, Siddha, Unani and in other Asian traditional systems. The aerial part of the plant is used in the form of infusion, raw juice, powder and decoction either alone or in combination with other medicinal plants. *Andrographis paniculata* is given in the form of tablets in Indian system of medicine and injection form in Chinese medicine for the treatment of common flu, swine flu, chikungunya, malaria and other viral fevers. A detailed comprehensive survey on *Andrographis paniculata* including the phytoconstituents and biological activities was done manually and electronically from pharmacopoeial monographs, journals, books, data bases of medicinal plants from 1986 to 2015 to provide a base for further research on this plant.

Keywords: *Andrographis paniculata*, King of bitters, traditional uses, pharmacological actions

Introduction
Andrographis paniculata (Burm. f.) Wall. ex Nees (Fig 1) belonging to the family Acanthaceae, is a medicinal plant traditionally used in India, China and southeast Asia for the treatment of cold, fever, sore-throat, diarrhoea and several infectious diseases [1]. *Andrographis paniculata* commonly known as Kalmegh, “King of bitters” in English, locally in Tamil Nadu, India it is called as *Nilavembu* or Siriyanangai and also known as *Bhui-neem*, meaning "neem of the ground", since the plant, has a similar strong bitter taste as that of the large neem tree. Though each part of the plant was used for different ailments, the aerial part is most commonly used [2]. *Andrographis paniculata* either in fresh or in dried form is commonly used by the local people, for the treatment of common cold, flu, malaria, diarrhoea, dysentery, cough, liver diseases, and snake bite [3] and in some skin infection. The plant is traditionally used as anti-bacterial, antioxidant, anti-diabetic, antipyretic, antiparasitic, antispasmodic, hepatoprotective, anti-inflammatory, anti-carcinogenic, antipyretic, antidiarrheal, nematicidal, anti-HIV and several infectious diseases ranging from malaria to dysentery [4]. *Andrographis paniculata* (powder and extract) is official in Indian Pharmacopoeia as kalmegh in 2007 [5] and in 2014 edition [6] and categorised as hepatoprotective agent. *Andrographis paniculata*/its extracts is also official in Chinese Pharmacopoeia [7] as Chuanxinlian tablet”, Chuan-Chin-Lian [8] “Andrographolide drop pill” and “Chuanxinlian capsule”.

Fig 1: Aerial parts of *Andrographis paniculata plant*

2. Traditional uses

Andrographis paniculata is a potential medicinal plant used in Ayurveda, Siddha and in Unani systems of medicine for the treatment of various infectious diseases, diabetes, liver cancer and malaria etc. In China, India, Thailand and Malaysia, this plant has been widely used for treating sore throat, common cold, flu and upper respiratory tract infections [9]. In Chinese medicine, it is used in the form of tablets and injections as Kan Jang tablets, Chuanxinlian tablets, Xiaoyan tablets and Yamdepieng injection and Chuanxialan ruang as injection respectively [7]. In Ayurvedic system of medicine it is used as carminative, liver stimulant, immune system stimulant, anthelmintic, blood purifier, anti-inflammatory, antipyretic, anti-malarial, anti-inflammatory and in prevention of infections [10]. In Siddha system of medicine it is used for treating cancer [11]. Government of Tamil Nadu officially distributes this plant extract through hospitals and health camps as nilavembu juice, nilavembu kudineer, nilavembu tonic, nilavembu kashayam, nilavembu choornam, nilavembu kudineer chooranam which mainly contains *Andrographis paniculata* either alone or with neem or papaya juice/extract for the management of malarial fever, dengue fever, chikungunya and common flu. *Andrographis paniculata* is also an ingredient in several polyherbal preparations used as hepatoprotectants [12] and has been reported to be effective in chronic hepatitis B virus infection [13]. The medicinal value of this plant is due to the presence of a bitter active ingredient andrographolide which is a bicyclic diterpenoid lactone derivative [14]. In the Unani system of medicine, it is considered as aperient, anti-inflammatory, emollient, astringent, diuretic, emmenagogue, liver tonic, carminative, anthelmintic and antipyretic. Due to its "blood purifying" activity it is recommended for use in cases of leprosy, gonorrhea, scabies, boils, and skin eruptions, chronic and seasonal fevers [15].

3. Phytoconstituents of *Andrographis paniculata*

Several active constituents reported to be present in *Andrographis paniculata* include flavonoids, flavonoid glycosides, diterpenes glycosides, lactones and diterpenes are the major active constituents. Flavonoids mainly exist in the root, but have also been isolated from the leaves. Bitter principle andrographolide in pure form was first isolated by Gorter *et al.* [16] where andrographolide was found to be high in leaves and hence most of the study are reported for leaves, compared to other parts of the plant [17]. Two main flavonoids, namely 5,7,2',3'-tetramethoxyflavanone and 5-hydroxy-7,2',3'-trimethoxyflavone were reported in *Andrographis paniculat*a [18]. Xu *et al.* [19] investigated and isolated 28 compounds from 80% ethanol roots of *Andrographis paniculata*. Twenty flavonoids three diterpenoids: two phenylpropanoids and beta-daucosterol. The compound 5,5'-dihydroxy-7, 8, 2'-trimetroxyflavone is new flavones isolated first time from this plant. Li *et al.* [20] isolated flavonoid glycosides 5-hydroxy-7,8-dimethoxy (2R)-flavanone-5-O-beta-D-glucopyranoside and 5-hydroxy-7,8,2',5'-tetramethoxy-flavone-5-O-beta-D-glucopyranoside, deoxyandrographolide-19 beta-D-glucoside and a new diterpenoid, andrographic acid along with andrographidine A from *Andrographis paniculata*. Chang *et al.* [21] identified two bitter principles andrographolide and a compound named kalmegh in leaves. The most important diterpenes reported in this plant are andrographolide, neoandrographolide, dehydroandrographolide and 14-deoxyandrographolide with wide range of therapeutic applications [22]. Other diterpenes reported in this plant are 14-deoxy-11,12-didehydroandrographolide, andrograpanin, andropanoside, 14-deoxy-12-methoxy-andrographolide, 14-di-deoxyandrographolide, 19-hydroxy-8, 13-labdadien-15, 16-olide, 3-oxo-14-deoxy-andrographolide, isoandrographolide, bisandrographolides, deoxy andrographolide, 14-deoxy-11, 12-didehydroandrographiside, andrographiside, 14-epi-andrographolide, isoandrographolide, 14-deoxy-12-methoxyandrographolide, 12-epi-14-deoxy-12-methoxyandrographolide, 14-deoxy-12-hydroxy andrographolide and 14-deoxy-11-hydroxy andrographolide [23, 24]. Diterpenes glycosides reported in this plant are 3-O-beta-D-glucosyl-14-deoxyandrographiside and 3-O-beta-D-glucosyl-14-deoxy-11,12-didehydroandrographiside [25]. Deoxyandrographolide-19-beta-D-glucoside, a diterpene glucoside from leaves, six diterpenoids of the ent-labdane type, two diterpene glucosides and four diterpene dimers (bis-andrographolides A, B, C and D) have been isolated from aerial parts of *Andrographis paniculata* [26].

4. Chemistry of andrographolide

Andrographolide is a colourless crystalline solid with bitter taste was first isolated by Gorter [16] in the year 1911 from the plant *Andrographis paniculata*. The chemical name of andrographolide is 3-[2-[decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1-napthalenyl] ethylidene]dihydro- 4-hydroxy-2(3H)-furanone. Andrographolide (Fig 2) (Molecular formula $C_{20}H_{30}O_5$, Mol. weight 350.45 g; melting point 230-231 ºC) is the major phytoconstituent mainly concentrated in leaves of *Andrographis paniculata* contains an α-alkylidene-γ-butyrolactone moiety (labdane-diterpenoid lactone), two double bonds at 8th and 12th position ($\Delta^{8(17)}$ and $\Delta^{12(13)}$), two methyl groups at C-4 (β-configuration) and C-10 (α-configuration) position, carbonyl group at C-16 position, oxygen hetero atom between C-15 and C-16 position, three hydroxyl groups at C-3, C-14 and C-18 positions where the first two hydroxyl groups at C-3 and C-14 are secondary in nature and the hydroxyl group at C-18 is primary in nature.

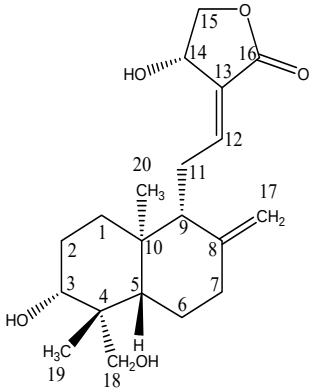

Fig 2: Structure of Andrographolide

5. Physicochemical Properties

Physicochemical characterization of plant or its extract/powder is important part of analysis for its identity and purity for using it for the formulation development. Pharmacopoeial limits [27, 28, 29] of physicochemical standards of *Andrographis paniculata viz*. foreign organic matter, loss on drying, total ash, acid insoluble ash, water soluble ash, water soluble extractive value, alcohol soluble extractive value, pesticide residue, radioactive residue, heavy metals and microbial contaminations were provided in Table 1.

Table 1: Physicochemical standards of aerial parts of *Andrographis paniculata*.

Parameters	WHO	USP	IP	Ameh *et al.* 2010 [28]	Kaskoos *et al.* 2014 [29]
Description	Dried aerial parts	Greyish brown powder	Intensely bitter taste	Dry, dark green aerial parts, practically odourless	Aerial parts
Foreign organic matter	NMT 2%	NMT 2%	NMT 2%	----	----
Alcohol soluble extractive	NLT 13% using ethanol 85%	NLT 8%	NLT 3%	---	13.18±1.38%
Water soluble extractive	NLT 18%	-----	NLT 12%	30.37±2.63	19.43±1.42%
Total ash	---	NMT 15%	NMT 15%	14.10±4.49	11.64±0.92%
Acid insoluble ash	---	NMT 3%	NMT 3%	1.00±0.06	1.3±0.27%
Loss on drying	NMT 2%	NMT 12%	NMT 12%	10.64±0.36	4.73±1.64%
Microbial contamination	----	Total aerobic bacterial count not to exceed 10^3cfu/g Total combined molds & yeasts count not to exceed 10^3cfu/g	Complies with microbial contamination tests	-----	-----
Heavy metals Lead Cadmium Arsenic	-----	20 ppm	20 ppm	----	-----
Pesticide residue	0.05 mg/kg	Meets the requirements	----	----	----

6. Pharmacological activities of *Andrographis paniculata*

6.1. Analgesic activity

Analgesic, antipyretic and anti-inflammatory activity of nilavembu kudineer was evaluated by Ghosh *et al.* [30], where the authors reported that oral administration of nilavembu kudineer (20 to 30 mL/kg) elicited analgesic and anti-inflammatory activity only but failed to produce antipyretic activity. Analgesic, antipyretic, anti-inflammatory and toxic effects of andrographolide derivatives in experimental animals were reported [31, 32]. Lin *et al.* [33] reported on analgesic activities of *Andrographis paniculata* extracts and their active constituent andrographolide.

6.2. Anti-Pyretic activity

Amaryan *et al.* [34] reported a double blind, placebo controlled, randomised pilot clinical trial of standardised fixed combination of *Andrographis paniculata* with *Eleutherococcus senticosus, Schisandra chinensis and Glychrrizhia glabra* for familial Mediterranean fever in two parallel groups of patients. Antipyretic, anti-inflammatory and analgesic properties of nilavembu kudineer chooranam: a classical preparation used in the treatment of chikungunya fever was reported by Anbarasu *et al.* [35]. Madav *et al.* [36] reported that andrographolide not showed any analgesic activity in hot plate test in mice while it showed significant ($p < 0.05$) analgesic activity in acetic acid-induced writhing in mice and Randall test in rats at 300 mg/kg dose. Authors also reported that andrographolide at 100 and 300 mg/kg, oral dose elicited significant ($p < 0.05$) antipyretic effect after 3 h of administration in Brewers yeast-induced pyrexia in rats and significant ($p < 0.05$) anti-ulcerogenic activity in aspirin induced ulceration in rats.

6.3. Anti-inflammatory activity

Andrographis paniculata extracts and their phytoconstituents reported to exhibit anti-inflammatory activity by inhibiting nitric oxide and prostaglandin production. Anti-inflammatory effects of dimethylbenzene-induced ear edema in mice and the Structure activity relationship of andrographolide and its derivatives were investigated by Gui-Fu *et al.* [37] and the mechanism of activity described may be due to inhibition of NO and PGE_2 production. Batkhuu *et al.* [38]. Isolated diterpene lactones, neoandrographolide from the methanol extract of *Andrographis paniculata* and recorded a concentration dependant anti-inflammatory activity. Abu-Ghefreh *et al.* [39] reported *in vitro* and *in vivo* anti-inflammatory effects of andrographolide, where the ability of andrographolide to inhibit the release of inflammatory cytokines was investigated. Burgos *et al.* [40] reported anti-inflammatory effects for *Andrographis paniculata*, attributed to the main constituent andrographolide proposed as alternative in the treatment of autoimmune disease. Authors performed prospective, randomized, double blind, and placebo-controlled study in patients with rheumatoid arthritis (RA). Tablets (Paractin) made of an extract of *Andrographis paniculata* (30% total andrographolides) were administered three times a day for 14 weeks, after a 2-week washout period to 60 patients with active RA. Reduction of rheumatoid factor, IgA, and C4 findings suggested that *Andrographis paniculata* could be a useful "natural complement" in the treatment of RA. Liu *et al.* [41]. Reported i*n vivo* and *in vitro* anti-inflammatory activities of neoandrographolide, where significant reduction of ear edema was observed in mice after edema induced by administration of dimethyl benzene. Maria *et al.* [42]. Proposed there main possible mechanism for the anti-inflammatory effects of andrographolide, where the first one is involved in the reduction of COX-2 expression by andrographolide in neutrophils comprises the modulation of the NF-κB pathway. The second mechanism describes an inhibitory effect of andrographolide on iNOS and COX-2 expression in macrophages, which in turn transform transcription factors AP-1 and STAT3 which are important for the production of pro-inflammatory cytokines such as IL-1β, IL-6 and IL-10. The third mechanism involves the interference of the transcription factor Nuclear Factor of Activated T cells induced by andrographolide in T-cells.

Warisara *et al.* [43] established anti-inflammatory activities of diterpenoids dehydroandrographolide, andrographolide and neoandrographolide isolated from *Andrographis paniculata*, where authors concluded that activity may be due the suppression of production of inflammatory cytokines and COX. Ethyl acetate extract of *Andrographis paniculata* displayed inhibitory activity on LPS-induced acute inflammation and on NF-kappa B trans-activation in mice [44]. Zhang *et al.* [45] reported a novel andrographolide derivative (CHP1002), inhibited pro-inflammatory inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in RAW264.7 macrophages via up-regulation of heme oxygenase-1 expression. Li *et al.* [46] reported synthesis of andrographolide derivatives and their TNF-α and IL-6 expression inhibitory effects in mouse macrophages were evaluated. Authors concluded most of the tested compounds showed inhibitory effects, and the compound 12-hydroxy-14-dehydroandrographolide showed better inhibitory activity than isoandrographolide. Lee *et al.* [47] reported andrographolide elicited anti-inflammatory activity in LPS-stimulated RAW 264.7 macrophages by inhibiting STAT3-mediated suppression of the NF-B pathway. Anti-inflammatory activity of new compounds from *Andrographis paniculata* by N-F-κB transactivation inhibition was reported by Chao *et al.* [48]. Xia *et al.* [49] reported a possible mechanism of action for the anti-inflammatory of andrographolide. It was found during their screening for the activity that it formed a covalent adduct with reduced cysteine (62) of p50, thus blocking the binding of NF-kappaB oligonucleotide to nuclear proteins and thus NF-kappaB activity was potently inhibited by andrographolide. Wen-Fei *et al.* [50] reported andrographolide suppressed inducible nitric oxide synthase expression in RAW 264.7 cells by prevention of the de novo protein synthesis and decreasing the protein stability via a post-transcriptional mechanism.

6.4. Anti-Cancer activity

Andrographis paniculata and its major phytoconstituent andrographolide reported to exhibit anticancer activity by various mechanism of actions *viz*. increasing cell differentiation [51], increasing tumor suppressor proteins p53 and p21 [52], decreasing proliferation of cancer cells [53], increase in IL-2 and IFN-c [46] and decreasing tumour growth and cell cycle arrest at G2/ phase. Nanduri *et al.* [54] performed semi-synthetic studies leading to the preparation of a number of potent and novel analogues of andrographolide, where analogue 8,17-epoxy andrographolide retained the cytotoxic activity. Introduction of hydrophilic groups at C-12 position of andrographolide did not enhance the cytotoxic effect, whereas single substitution of aromatic ring at this position showed moderate cytotoxic activity [55]. Cytotoxic activities of major diterpenoid constituents of *Andrographis paniculata* in human tumor cell lines was reported by Tan *et al.* [56].Cheung *et al.* [57] reported *in vitro* cytotoxicity of the ethanol extract of *Andrographis paniculata* and active constituents found that it significantly inhibited the growth of human acute myeloid leukemic HL-60 cells with an IC_{50} 14.01 µg/mL after 24 h of treatment. The cytotoxicity of andrographolide to HepG2 human hepatoma cells was investigated by Li *et al.* [58] where andrographolide elicited IC_{50} value of 40.2 µM after 48 h of treatment. Andrographolide was identified as radio sensitizing agent with potential application in cancer radiotherapy and a possible molecular mechanisms of andrographolide-mediated radio sensitization was reported by Hung *et al.* [59]. Andrographolide treatment significantly reduced protein level of activated Akt and radiation-induced NF-kappaB activity. Effects of andrographolide and 14-Deoxy-11,12-Didehydroandrographolide on CYP1A2, CYP2D6 and CYP3A4 expressions in HepG2 cells was investigated [60], where both of them inhibited the mRNA and protein expressions of CYP1A2, CYP2D6, and CYP3A4. Ajaya Kumar *et al.* [61] reported on the anticancer and immunostimulatory compounds from *Andrographis paniculata* in human cancer and immune cells. Chen *et al.* [62] reported synthesis and *in vitro* cytotoxicity evaluation of series of andrographolide-19-oic acid derivatives and there *in vitro* antitumor activity against two human cell lines HCT-116 and MCF-7 cell lines, respectively. Bimolendu Das *et al.* [63] reported synthesis, cytotoxicity in human leukemic cell lines and structure–activity relationship (SAR) studies of a series of analogues of andrographolide, prepared through chemo-selective functionalization at C_{14} hydroxy group.

Li *et al.* [46] isolated andrographic acid from *Andrographis paniculata* and evaluated for cytotoxicity to KB cells along with andrographolide, isoandrographolide, neoandrographolide and 14-deoxy-11,12-didehydroandrographolide. Ranjan Preet *et al.* [64] synthesized novel andrographolide analogues and screened *in vitro* activity against kidney (HEK-293) and breast (MCF-7) cancer cells by MTT, immunostaining, FACS, western blotting and transcriptional inhibition of NF-kB activity. Wei *et al.* [65] synthesized seventeen derivatives of andrographolide by esterification and etherification of 14-dehydroxy-11,12-didehydroandrographolide and demonstrated significant inhibition against tumor cell growth. Shi *et al.* [66] reported inhibition of cell-cycle progression in human colorectal carcinoma Lovo cells by andrographolide. Novel plant-derived andrographolides were screened for antineoplastic activity by Varma *et al.* [67]. Rajagopal *et al.* [68] reported *in vitro* anticancer activity of andrographolide in human cancer and immune cells, where 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. Immunostimulatory activity of andrographolide is evidenced by increased proliferation of lymphocytes and production of interleukin-2. Jada *et al.* [69]. Synthesized andrographolide analogues 3,19-isopropylideneandrographolide, 14-acetyl-3,19-isopropylideneandrographolide and 14-acetylandrographolide and evaluated their *in vitro* antitumour activities against MCF-7 (breast cancer cell line) and HCT-116 (colon cancer cell line). Matsuda *et al.* [70] isolated six new diterpenoids of ent-labdane type from the ethyl acetate-soluble fraction of the methanol extract of *Andrographis paniculata* and four new diterpene dimers and reported to exhibit the anticancer activity by inducing cell differentiation in M1 cells. Zhao *et al.* [71] reported on Anti-tumour activities of andrographolide, a diterpene from *Andrographis paniculata*, by inducing apoptosis and inhibiting VEGF level. Iruretagoyena *et al.* [72]. Reported 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 in the mouse. Sheeja *et al.* [73] reported *Andrographis paniculata* extract and its isolated compound andrographolide on cell-mediated immune responses in normal and tumor-bearing control animals significantly enhanced natural killer cell activity. Yang *et al.* [74] reported Andrographolide Induces Apoptosis of C6 Glioma Cells via the ERK-p53-Caspase 7-

PARP Pathway. Suppression of the adhesion of gastric cancer cells through E-selectin expression was observed for andrographolide [75].

6.5. Hepatoprotective activity

Andrographis paniculata exerted hepatoprotective effect by decreasing the ALT activity [76], decreasing liver injury and hepatocyte apoptosis[12] decreasing GOT, GPT, ACP, and ALP levels and loss of HBsAg, HBeAg, and HBV DNA [77].Absorption of andrographolides from *Andrographis paniculata* and its effect on CCl_4-induced oxidative stress in rats was reported by Akowuah *et al*. [78]. Jarukamjorn *et al*. [79] reported the impact of *Andrographis paniculata* crude aqueous and ethanol extract on mouse hepatic cytochrome P450 enzymes, where the total hepatic P450 content was not significantly modified by aqueous or the alcoholic extracts of *Andrographis paniculata*. Authors suggested that *Andrographis paniculata* might effectuate hepatic cytochrome P450 enzymes of which CYP1A1 and CYP2B are the responsive P450 isoforms. Yan Pan *et al*. [80] reported i*n vitro* effect of important herbal active constituents andrographolide, asiaticoside, asiatic acid, madecassic acid, eupatorin, sinensetin, caffeic acid, and rosmarinic acid on human cytochrome P450 1A2 (CYP1A2) activity. Andrographolide and neoandrographolide at 6 mg/kg/day for two weeks, alcohol extract of Chao *et al.* [81] reported on the hepatoprotective activity of diterpenoids, isolated from *Andrographis paniculata*. Trivedi *et al.* [82]. Reported hepatoprotective and antioxidant property of *Andrographis paniculata* (Nees) in BHC induced liver damage in mice. Pekthong *et al*. [83] reported on effects of *Andrographis paniculata* extract and andrographolide on hepatic cytochrome P450 mRNA expression and monooxygenase activities in rats. Choudhury *et al*. [84, 85]. Reported oral administration of kalmegh extract exhibited hepatoprotection of alcohol-induced and carbon tetrachloride-induced toxic-effect in liver tissue. Rana *et al.* [86] reported hepatoprotective action of *Andrographis paniculata* extract against carbon tetrachloride-induced liver damage. Handa *et al.* [87]. Also reported hepatoprotective activity of andrographolide against carbon tetrachloride, galactosamine & paracetamol intoxication in rats. Hepatoprotective activity was monitored by estimating the serum transaminases (GOT and GPT), alkaline phosphatase and bilirubin in serum, hepatic triglycerides, and by histopathological changes in the livers of experimental rats. Authors concluded that the activity may be due to the hepatoprotective constituent andrographolide in *Andrographis paniculata*. Visen *et al.* [88] observed a significant dose dependent (0.75-12 mg/kg *p.o.* x 7) protective activity for andrographolide against paracetamol-induced toxicity on ex vivo preparation of isolated rat hepatocytes. Pekthong *et al.* [89] examined the effect of plant extract and andrographolide on hepatic cytochrome P450s (CYPs) of rat and human liver microsomes. Kapil *et al.* [90] reported on antihepatotoxic effects of major diterpenoid constituents of *Andrographis paniculata* on hepatotoxicity induced in mice by carbon tetrachloride or tert-butyl hydroperoxide (tBHP) intoxication. Trivedi *et al.* [91] reported on hepatoprotective effect of andrographolide against hexachlorocyclohexane-induced oxidative injury. *Andrographis paniculata* and *Swertia chirata* extract at a dose of 100 and 200 mg/kg exhibited hepatoprotective action in mice [92]. The elevated levels of the serum marker enzymes due to the administration of paracetamol, restored to normal level after oral administration of these extracts.

6.6. Anti-diabetic activity

Anti-diabetic property of ethanol extract of *Andrographis paniculata* in streptozotocin-diabetic rats was reported to decrease blood glucose level [93, 94] and 49.8% fasting triglyceride levels [95]. Hypoglycaemic effect of aqueous extract *Andrographis paniculata* at a dose of 10 mg/kg after inducing hyperglycaemia by oral administration of glucose 2 mg/kg in rabbits was investigated by Borhanuddin *et al*. [96]. Koteswara Rao [97] reported antihyperglycemic activity in alloxan induced diabetic rats for chloroform root extract of *Andrographis paniculata*. Alpha-glucosidase inhibitory activity for semi-synthetic derivatives of andrographolide [98], hypoglycemic and beta cell protective effects of andrographolide analogue, andrographolide-lipoic acid conjugate was reported [99]. Nugroho *et al*. [100] reported anti-diabetic and antihyperlipidemic effect of *Andrographis paniculata* (Burm. f.) Nees and andrographolide in high-fructose-fat-fed rats. The study showed that the treatment of the high-fructose fat consisting of 36% fructose, 15% lard, and 5% egg yolks in 0.36 g/200 g BW for 55 days succeeded to stimulate blood glucose, triglyceride, and LDL levels in comparison to the control. The diet also moderately increased the blood cholesterol and rat body weight. A dose dependent antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats was observed in a study suggested that andrographolide can increase the glucose utilization to lower plasma glucose in diabetic rats lacking insulin [101]. Reyes *et al.* [102] reported anti-diabetic potentials of *Momordica charantia* and *Andrographis paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats. Subramanian *et al.* [103] reported significant *in vitro* alpha-glucosidase activity in a concentration dependant manner and weak alpha-amylase enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide. *In vivo* studies of the extract and andrographolide also demonstrated significant reduction in blood glucose level in diabetic rats.
Wibudi *et al.* [104] examined the effect of *A. paniculata* on pancreatic β-cells and stated that it exhibited a very strong, dose dependent insulinotropic, glucose dependent and independent insulin secreting action.

6.7. Immunomodulatory activity

Andrographis paniculata showed immunomodulatory activity by increasing antibody production decreasing delayed-type hypersensitivity response, increasing proliferation of human peripheral blood lymphocytes and key cytokines and the expression [105]. Panossian *et al.* [106] reported *in vitro* immunomodulatory effect for andrographolide and Kan Jang by production of key cytokines and immune activation markers and by inhibition of spontaneous proliferation of peripheral blood lymphocytes. Radhika *et al*. [107] reported significant immunostimulant, cerebroprotective and nootropic activities for leaf extract of *Andrographis paniculata* in normal and type 2 diabetic rats. Naik *et al.* [108] demonstrated andrographolide has the ability to enhance immune function, where a significant increase in total WBC count and relative increase in weight of spleen and thymus was observed in mice during 30 days of treatment.

6.8. Anti-platelet activity

Phytoconstituents and extracts of *Andrographis paniculata* was reported to exhibit anti-platelet activity by various mechanism of actions *viz*. decreasing platelet activating factor [109] and increasing eNOS-NO/cyclic-GMP pathway by

decreasing PLCγ2-PKC and PI3 kinase/Akt-MAPKs [110]. Inhibitory effect of *Andrographis paniculata* extract and its active diterpenoids on platelet aggregation was studied by Thisoda *et al.* [111]. The results indicated that andrographolide and 14-deoxy-11, 12-didehydroandrographolide significantly inhibited thrombin-induced platelet aggregation in a concentration and time-dependent manner while neoandrographolide had little or no activity. The results indicated that the standardized *Andrographis paniculata* extract may contain other anti-platelet compounds, which contribute to high anti-platelet activity. Amroyan *et al.* [112] tested andrographolide for PAF-induced platelet aggregation, where, andrographolide inhibited PAF-induced human blood platelet aggregation in a dose dependent manner (IC50 ~5 μM). These results indicated that andrographolide has a mechanism of action different from that of non-steroidal anti-inflammatory drugs (NSAID) and most likely associated with the cardiovascular and antithrombotic activity described of *Andrographis paniculata.* Wu *et al.* [113] isolated two new flavones designated as andropaniculosin A and ropaniculoside A and 30 known compounds from the whole plants of *Andrographis paniculata*.

7. Biological activities of *Andrographis paniculata*

7.1. Anti-bacterial activities

Andrographis paniculata acted against nine bacterial strains such as *Salmonella typhimurium, Escherichia coli, Shigella sonnei, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumonia, Streptococcus pyogenes, Legionella pneumophila,* and *Bordetella pertussis* [114]. Jiang *et al.* [115] reported synthesis and evaluated anti-bacterial activities of andrographolide analogues and suggested a possible mechanism of action. Ahmed *et al.* [116] attempted to identify and isolate pure anti-bacterial compounds from the methanol extract of the whole plant of *Andrographis paniculata* through bioassay guided isolation method, where they have demonstrated antibacterial activity for 3-*O*-β-D-glycosyl-14-deoxyandrographolide.

7.2. Antifungal activity

Antifungal activity was studied [117] for dichloromethane and methanol extracts of *A. paniculata* by broth micro dilution method against seven pathogenic fungal species. Dichloromethane extract of *A. paniculata* exhibited lowest minimum inhibitory concentration (MIC) (100 μg/mL) against *Microsporum canis, Candida albicans*, and *Candida tropicalis*, whereas methanol extract revealed lowest MIC (150 μg/mL) against *C. tropicalis* and *Aspergillus niger*. Methanol extract of the aerial parts of the *Andrographis paniculata* exhibited mycelial growth inhibition of *Fusarium solani* and spore germination inhibition of *Alternaria solani* [118].

7.3. Anti-viral activity

Andrographis paniculata reported for anti-viral activity against herpes simplex virus 1 (HSV-1) [119, 120], flaviviruses and pestiviruses and Dengue virus (DENV1).Tang *et al.* [121] investigated anti-viral activity for methanol extracts of medicinal plants viz. *Andrographis paniculata, Citrus limon, Cymbopogon citratus, Momordica charantia, Ocimum sanctum* and *Pelargonium citrosum* on dengue virus serotype 1 (DENV-1). Anti-viral assay based on cytopathic effects (CPE) denoted by degree of inhibition upon treating DENV1-infected Vero E6 cells with MNTD of six medicinal plants showed that *A. paniculata* has the most anti-viral inhibitory effects followed by *M. charantia.*

Lin *et al.* [122] reported on Inhibition of the epstein-barr virus lytic cycle by andrographolide. *Andrographis paniculata* Nees is a medicinal plant that is commonly used in Asia.

7.4. Anti-HIV activity

Novel bis-andrographolide ether and six known compounds andrographolide, 14-deoxy-11,12-didehydroandrographolide, andrograpanin, 14-deoxyandrographolide, 5-hydroxy-7,8-dimethoxyflavanone and 5-hydroxy-7,8-dimethoxyflavone have been isolated from the aerial parts of *Andrographis paniculata* were tested for the anti-HIV and cytotoxic activity by Reddy *et al.* [123]. Calabrese *et al.* [124] conducted phase I trial of andrographolide in 13 HIV positive patients and 5 normal volunteers and assessed safety, tolerability and the effects on plasma virion HIV-1 RNA levels and CD4(+) lymphocyte levels. No statistically significant changes were observed in mean plasma HIV-1 RNA levels throughout the trial. It was suggested that andrographolide may inhibit HIV-induced cell cycle dysregulation, leading to a rise in CD4(+) lymphocyte levels in HIV-1 infected individuals. Chang *et al.* [125]. Reported on Dehydroandrographolide succinic acid monoester as an inhibitor against the human immunodeficiency virus. Neoandrographolide exhibited prohormone proprotein convertase (PC)-inhibitory properties with anIC_{50} of 53.5 lM against furin [126]. It is suggested that it possibly acts by suppressing the proteolytic cleavage of envelope glycoprotein gp160 of HIV, which is known to be PC-mediated, particularly by furin and PC7.A series of andrographolide derivatives was synthesized and evaluated for anti-HIV activity in TZM-bl cells. 3-Nitrobenzylidene derivative showed higher *in vitro* anti-HIV activity compared to andrographolide [127]. Wirat *et al.* [128] tested virucidal activity for andrographolide, neoandrographolide and 14-deoxy-11,12-didehydroandrographolide, ent-labdene diterpenes isolated from *Andrographis paniculata* against herpes simplex virus 1 (HSV-1). None of these compounds exhibited significant cytotoxicity at viricidal concentrations.

7.5 Anti-malarial activity

Widyawaruyanti *et al.* [129] reported *in vivo* anti-malarial activity for *Andrographis paniculata* tablets.Anti-malarial activity was tested for *Andrographis paniculata* extracts along with 3 other plants by lactate dehydrogenase assay [130]. Dua *et al.* [131]. reported on anti-malarial activity of some xanthones isolated from the roots of *Andrographis paniculata*. Mishra *et al.* [132]. reported on anti-malarial activities of *Andrographis paniculata* and *Hedyotis corymbosa* extracts and their combination with curcumin. Anti-malarial activity of *Andrographis paniculata* along with *Goniothalamus scortechinii* and *Aralidium pinnatifidum* was evaluated by lactate dehydrogenase assay in *Plasmodium falciparum* [133] where all the extracts exhibited the growth inhibitory action of malarial parasite.

7.6. Anti-dengue activity

Tang *et al.* [121]. Reported anti-dengue activity in methanol extracts of medicinal plants of *Andrographis paniculata*, *Citrus limon*, *Cymbopogon citratus*, *Momordica charantia*, *Ocimum sanctum* and *Pelargonium citrosum* on dengue virus serotype 1 (DENV-1). Authors reported methanol extracts of *Andrographis paniculata* and *M. charantia* possess the ability of inhibiting the activity of DENV-1 whereas *C. limon* and *P.*

citrosum did not prevent cytopathic effects or cell death of DENV-1. Kalaiarasi *et al.* [134]. Reported that administration of combination of Nilavembu Kudineer and Adathodai Manapagu for scheduled period of 7 days in 20 cases revealed satisfactory symptomatic relief and significant improvement in the management of dengue fever.

8. Acute and sub-acute toxicity studies of andrographolide

No death or hazardous signs were observed from acute and sub-acute toxicity study of andrographolide tested in both male and female mice upto a dose 5 g/kg body weight [135].

9. Adverse effects

On overdosing of *Andrographis paniculata* extract caused vomiting, gastric discomfort and loss of appetite that may be due to very high bitter taste of the herb [136]. Though this plant or its extract is safe, it is not to be taken during pregnancy as it is classified under class 2b in botanical safety hand book [137].

10. Conclusions

Andrographis paniculata is one of the most important medicinal plants used widely in traditional system of medicine, having potent pharmacological activities. Though many review articles are available and described about the traditional uses, phytochemistry and pharmacology of the plant, none of them described about the complete details on this plant and hence a systematic comprehensive review of the plant is described here as it will facilitate the researchers working on this plant and also for the Government authorities for having in depth knowledge about the efficacy of *Andrographis paniculata*.

11. References

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