

# Andrographolide: its pharmacology, natural bioavailability and current approaches to increase its content in andrographispaniculata

## Abstract

Andrographolide is a labdane diterpenoid produced by *Andrographis paniculata* (AP) a predominant constituent of at least 26 Ayurvedic formulations used to treat liver ailments. The current yield of andrographolide is too low to meet the commercial goal of plant cell-based bioprocess for the production of most secondary metabolites. Attempts have been made by researchers to increase the andrographolide content in AP, however, none of these are able to meet the rising commercial demand of andrographolides. Poor bioavailability of andrographolide, owing to high lipophilicity is another stumbling block that renders the wonder drug uneconomical. Thus despite its myriads of medicinal properties, andrographolide still remains an unyielding natural compound. This review deals with the pharmacology of andrographolides, possibilities that have been worked out to increase the andrographolides content in AP and also increase its natural bioavailability.

**Keywords:** andrographolide, *andrographis paniculata*, bioavailability, pharmacology, anticancer, anti-inflammatory

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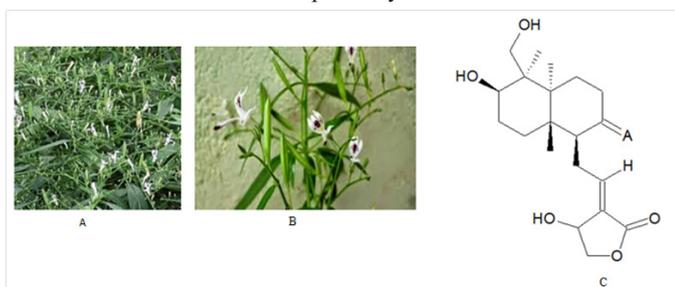
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## Introduction

Andrographolide is a labdane diterpenoid produced by *Andrographis paniculata*, (AP) a predominant constituent of at least 26 Ayurvedic formulations used to treat liver ailments. The plant produces a range of bioactive components like andrographolides and polyphenols.<sup>1</sup> Among these, andrographolides (Figure 1) are pharmacologically the most active compounds; however, andrographolide content in conventionally propagated or wild plants is estimated to be only 2%-3%. The conventional vegetative propagation of AP is too slow to meet the demand of pharmaceutical industries which is increasing annually at a rate of 3.1%. Owing to its multivariate medicinal uses, the plant is placed at 17<sup>th</sup> position among 32 prioritized medicinal plants of India with a demand of 2197.3tons.<sup>2</sup> The myriads of potential therapeutic effects of andrographolides have contributed to its rising price and market demand. Quality dry leaves of the plant are sold for as much as US \$5/kg, whilst the purified andrographolide and its derivatives could reach up to the US \$ 100,000/kg. The latest pricing by Sigma-Aldrich Corporation (USA) in 2016 for 100 and 500mg packages of andrographolide (98%) is US \$36.20 and the US \$ 135.00 respectively.



**Figure 1** *Andrographis paniculata* (A) Plant; (B) Flowers and fruits; (C) Andrographolide.

Most of the modern drug discovery could be attributed to traditional knowledge, and andrographolide is no different.<sup>3</sup> AP owes most of its

medicinal properties to the presence of andrographolides. The plant is reported to have antibacterial, antifungal, antiviral, choleric, hypoglycemic, hypocholesterolemic, and adaptogenic effects.<sup>4</sup> In the Unani system of medicine, the AP is believed to possess anti-inflammatory, antipyretic, emmenagogue, astringent, gastric and liver tonic, diuretic, carminative and antihelmintic properties. It is also recommended for curing leprosy, gonorrhoea, and various skin related disorders, owing to its "blood purifying" activity. Juice or an infusion of fresh leaves is effective in curing irregular bowel habits, and loss of appetite, mostly in infants.<sup>5</sup> Leaves and roots of the plant are also used in general debility, dyspepsia associated with gaseous distension, and in advanced stages of dysentery. In Chinese Medicine, the herb derived from the leaves or aerial parts of AP is known as Chuanxinlian, Yijianxi or Lanhelian and is known to possess similar properties, as described in Ayurveda, Unani or Traditional Indian Medicine. Various preparations and compound formulas of the herb have been used to treat infectious and non-infectious diseases, with significant efficacy reported in case of epidemic encephalitis B, neonatal subcutaneous annular ulcer, vaginitis, cervical erosion, pelvic inflammation, herpes zoster, chicken pox, mumps, neurodermatitis, eczema, and burns.<sup>6,7</sup>

## Current approaches to increase andrographolide content in AP

The current yield of andrographolide is too low to meet the commercial goal of plant cell-based bioprocess for the production of most secondary metabolites. Thus, in order to increase the yield, various techniques in plant cell-based processes are being critically studied. However, most often trials with plant cell cultures fail to produce the desired products. One of the main problems in increasing the production of secondary metabolites is the lack of basic knowledge of the biosynthetic routes and mechanisms responsible for the production of plant metabolites. The problem of limited productivity of desired metabolites due to lack of particular precursors can be tackled through bio transformation, using an exogenous supply of biosynthetic precursors; further, genetic manipulation,

and metabolic engineering may improve the accumulation of compounds. Andrographolide content varies within plant parts and with the geographical distribution. The andrographolide content in conventionally propagated or wild plants is estimated to be only 2%-3%.<sup>8</sup> The conventional vegetative propagation of AP is excessively slow to meet the demand of pharmaceutical industries. Variability among the seed derived progenies and delayed rooting of seedlings confines propagation through seeds.<sup>9</sup>

Thus attempts were made by many researchers to increase the quantity of andrographolide in AP plant parts using different inducers. Recently, the leaf biomass and the production of andrographolide compounds in AP were significantly increased after exogenous treatment with the synthetic cytokinin-1-(2-chloro-4-pyridyl)-3-phenylurea (CPPU) at 0, 5, or 10mg L<sup>-1</sup>, for 7days. CPPU significantly enhanced the formation of axillary bud and promoted branching by 4.6-5.6-fold, resulting in higher fresh weight (FW) and dry weight (DW). Though CPPU at 10mg L<sup>-1</sup> slightly caused leaf stress and chlorophyll reduction, a 5mg L<sup>-1</sup> CPPU enhanced the andrographolide content.<sup>10</sup>

Further, to meet the overgrowing demand of andrographolide by pharmaceutical companies, attempts were also made to multiply AP through tissue culture. Andrographolide induction in callus treated by Naphthalene Acetic Acid was achieved by Alwar et al.,<sup>11</sup> Valdiani et al.,<sup>12</sup> investigated the genetic mechanisms controlling the biosynthesis of andrographolides using a diallele analysis. The high-performance liquid chromatographic analysis confirmed that the biosynthesis of andrographolides was considerably increased through interspecific hybridization. Though there has been a continuous upsurge of technique intensive artificial means of increasing secondary metabolite production in AP, however, enhancement of andrographolide content through natural amendments is still unachieved.

## Bioavailability of andrographolide

### Natural bioavailability

The Biopharmaceutics Classification System (BCS), classified drugs into four categories, class I (high solubility, high permeability); class II (low solubility high permeability); class III (low solubility low permeability). Andrographolide belongs to class III, as per BCS.<sup>13</sup> The absolute bioavailability of AP was reported to be 2.67% and the drug metabolized to a sulfonate 14-deoxy-12-sulfo- andrographolide in duodenum and jejunum. The poor oral bioavailability of andrographolide is attributed to its high lipophilicity (log P value=2.632±0.135), low aqueous solubility (3.29±0.73mg/ml) rapid transformation and efflux by P-glycoprotein.<sup>14</sup>

### Distribution- major organ of absorption

The pharmacokinetic and oral bioavailability of AP has been thoroughly worked out by Panossian et al.<sup>15</sup> The study gave a systematic insight on its absorption, bioavailability, pharmacokinetics and elimination in rats and human systems. Andrographolide was quickly absorbed from the gastro-intestinal tract into the blood with an absorption half-life of about 25minutes. It then bound extensively to blood proteins and redistributed between blood and tissues within 1-2hours. The maximum concentration of drug was achieved after 1.36 hours of its administration.<sup>15</sup>

### Formulations and drug delivery systems tried

Liu et al.,<sup>16</sup> designed a biocompatible microemulsion of AP (BMAP) containing both fat-soluble and water-soluble constituents.

The pharmacokinetic results of the microemulsion showed that the AUC<sub>0-7</sub> and AUC<sub>0-∞</sub> values of BMAP were 2.267 and 27.156µg·mL(-1)·h(-1) respectively, and were about 1.41-fold and 6.30-fold greater than that of ethanol extraction, respectively. Self-micro emulsifying formulations composed of AP extract (11.1%), Capryol 90 (40%), Cremophor RH 40 (40%) and Labrasol (8.9%) were developed in liquid and pellet forms to improve the bioavailability of andrographolide in *in vivo* systems. The pharmacokinetic parameters like maximum concentration (C<sub>max</sub>), time to reach maximum concentration (T<sub>max</sub>) and the under concentration time curve (AUC<sub>0-12</sub>) were determined. The optimized formulations showed a significant increase in the dissolution of andrographolide, 97.64% and 97.74% within 15min from liquid and pellet formulations respectively as compared to the crude extract powder (10% within 2h) (p<0.05). The AUC<sub>0-12</sub> of andrographolide (for the same dose equivalent of 35mg/kg of andrographolide) from liquid and pelleted formulations was 9 and 26 fold higher as compared to the unformulated extract. The C<sub>max</sub> of andrographolide in liquid SMEDDS and SMEDDS pellets was 6 fold and 5 fold respectively; however, the T<sub>max</sub> of andrographolide from liquid and pelleted SMEDDS was similar to that of AP extract. The formulations were found to improve the dissolution and oral bioavailability of andrographolide thus enabling a reduction in the dose of the sparingly soluble AP extract.<sup>17</sup> Engineered nano-systems prepared by pre-electrolyte deposition of chitosan biopolymer on AP with poly lactic-co-glycolic acid (PLGA) were developed for smart recovery in hepatotoxic conditions. A rapid *in vitro* dissolution of the nano-system occurred up to 8 hours followed by a sustained effect for 432hours. The nano system showed improved biocompatibility and permeability necessary for pre-oral activity. A pre-treatment with the drug resulted in increased activity in the CCl<sub>4</sub> damaged antioxidant enzymes. It also reduced the release of pro-inflammatory cytokines IL-6 and TNFα in CCl<sub>4</sub> damaged liver tissues, thus protecting the liver by inducing hepatocyte proliferation and modulating the release of tissue-repair mediators.<sup>18</sup> Chellampillai et al.,<sup>19</sup> developed a system of pH-sensitive nanoparticles by a nanoprecipitation technique using Eudragit EPO (cationic poly methacrylate Copolymer) for improving the bioavailability of andrographolide. The smaller size of the nanoparticle (255±9nm) as compared to the pure drug (49,461±7 nm) increased its oral bioavailability 2.2 fold as compared to pure drug.

### Metabolism of andrographolide

The reports on the metabolism of andrographolide in rats and human systems have been meager. The metabolic adducts of andrographolide can be categorized as sulfonic acid or sulfate type adducts, glucuronide conjugates, and creatinine adducts. Though sulfonic acid or sulfate type adducts have been mainly identified; seven glucuronide conjugates and two creatinine adducts (14-deoxy-12-(creatinine-5-yl)-andrographolide-19-O-?-D-glucuronide A & 14-deoxy-12-(creatinine-5-yl)-andrographolide-19-O-?-D-glucuronide B) were also reported in the metabolic transformation.<sup>20,21</sup> The major metabolite of andrographolide in rats was identified as 14-deoxy-12(R)-sulfo andrographolide which has anti-inflammatory effects.<sup>22,23</sup> About ten andrographolide metabolites, mainly sulfonic acid adducts and sulfate compounds have been isolated and identified. Eleven new urinary metabolites of andrographolide in human were identified as 3-O-sulfate and 19-O-β-glucuronide conjugates.<sup>24</sup> Six metabolites of andrographolide identified as sulfate ester compounds were reported by He et al.<sup>22</sup> Four sulfonate metabolites of andrographolide, 14-deoxy-12(R)- sulfo andrographolide, 14-deoxy-12(S)-sulfo andrographolide, 14-deoxy-12(R)- 9S andrographolide

and 14-sulfo isoandrographolide were identified by He et al.,<sup>22</sup> The studies suggest that metabolism of andrographolide takes place through multiple pathways.

### Excretion/elimination

Intensive drug metabolism was the major elimination route and the drug could not be detected after the eighth hour of administration. About 8.2% of the compound was eliminated through urine within 72hrs of administration, the elimination rate being, 0.028ml/min. More than 90% of the compound was eliminated through other ways, probably through metabolic transformation. The highest rate of elimination took place in the interval of 6-24hrs.<sup>15</sup>

## Pharmacology

### Anti-inflammatory activity

Andrographolide was found to inhibit the inflammatory responses produced by rat neutrophils. Pre-treatment with the compound (0.1±10mM) prevented N-formyl-methionyl-leucyl-phenylalanine (fMLP)-induced neutrophil adhesion and transmigration in a concentration-dependent manner. Further, the andrographolide

pretreatment significantly reduced fMLP-induced production of H<sub>2</sub>O<sub>2</sub> and O<sub>2</sub> and also decreased fMLP-induced expression of both CD11 and CD18, an essential integrin-mediated in neutrophil adhesion and transmigration. The study suggested that andrographolide prevented the reactive oxygen species (ROS) production through part modulation of protein kinase C-dependent pathway and thus affected the downregulation of Mac-1, essential for neutrophil adhesion and transmigration.<sup>25</sup> Another anti-inflammatory mechanism of andrographolide (Figure 2) involves inhibition of the activation of NF-kappaB, suppression of inducible nitric oxide synthase (iNOS) expression and inhibition of COX-2 expression in human fibroblast cells.<sup>26</sup> Andrographolide reduced the intensity of the peritoneal inflammation produced by acetic acid in mice, indicating its ability to inhibit the permeability of small blood vessels. It also affects important inflammatory mediators, such as eicosanoids and platelet-activating factor (PAF) in a dose-dependent manner (IC<sub>50</sub>~5µM).<sup>27</sup> Another major phytoconstituent of AP, 14-Deoxy-11,12-didehydroandrographolide, significantly inhibited the expression of proinflammatory cytokines/chemokines (TNF-α, IL-1β, IL-6, CCL-2/MCP-1, IFN-α, IFN-β, IFN-γ, MIP-1α, MIP-1β in lungs of mice infected with pathogenic influenza viruses, H5N1.<sup>28</sup>

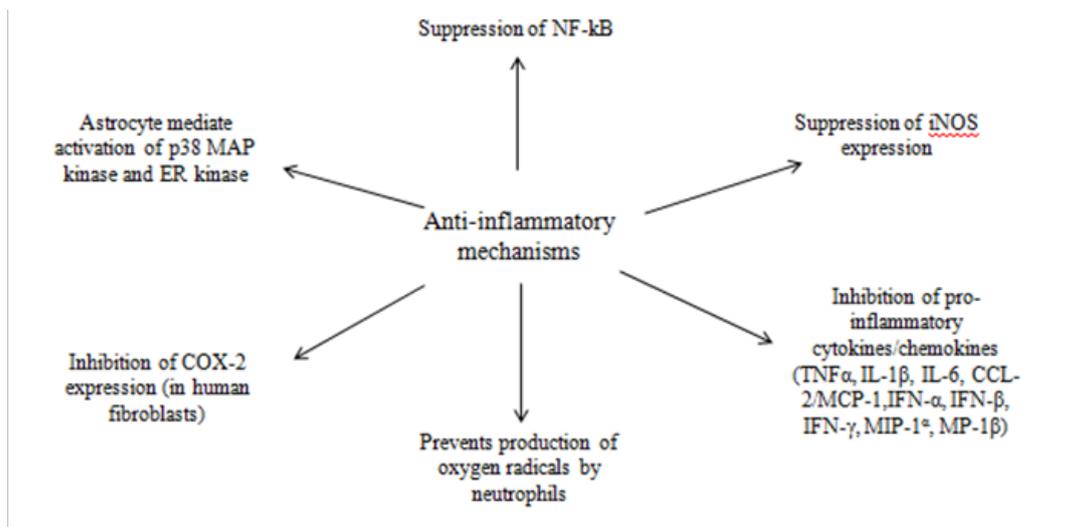


Figure 2 Anti-inflammatory mechanisms of andrographolide.

### Neuroprotective

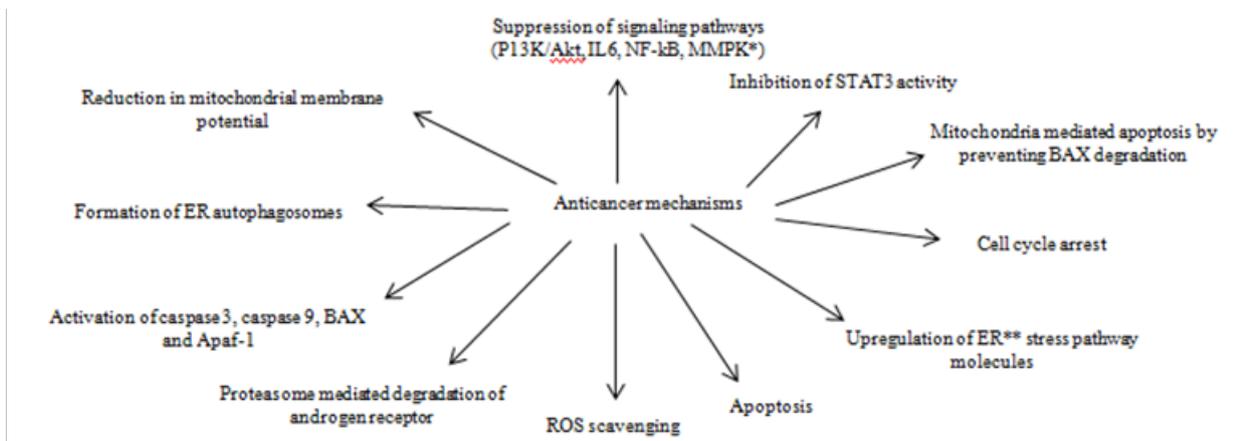
The neuroprotective effects of andrographolide were studied on RSC96 cells *in vitro*. The RSC96 cell line consisting of immortalized rat Schwann cell line were treated with varying concentrations of andrographolide (0 to 50µM), prior to the MTT assay. Cell proliferation, morphology, synthesis and nerve-specific gene expression were studied and andrographolide was found to be most effective between concentration range 0.78 and 12.5µM. The treatment increased DNA content and promoted the gene expression of glial cell line-derived neurotrophic factor, brain-derived neurotrophic factor, ciliary neurotrophic factor, and the specific Schwann cell marker S100β (P<0.05). Andrographolide accelerated the proliferation of RSC96 cells without altering the Schwann cell phenotype.<sup>29</sup> In another study, andrographolide potently activated NF-E2-related factor 2 (Nrf2) and also upregulated heme oxygenase-1 (HO-1) expression in primary astrocytes. Andrographolide reduced Nrf2, ubiquitination efficiency, and turnover rate, followed by upregulation of Nrf2 mRNA between 8 and 24h. HO-1 is a known gene target of transcription factor Nrf2, which is critically involved in cellular defence against oxidative

stress.<sup>30</sup> Andrographolide recuperated the cognitive impairment in the social species Octodon degus (the only wild-type South American rodent that develops Alzheimer's-like pathology with age), a natural model of Alzheimer's disease. The treatment resulted in the recovery of spatial memory and learning performance, recovery of synaptic basal transmission, partial or complete protection of certain synaptic proteins and reduction of phosphorylated tau protein and amyloid beta aggregate maturation in aged degus.<sup>31</sup> In a similar study, andrographolide increased neural progenitor cell proliferation and the number of immature neurons in the hippocampus of 2- and 10-month-old mice compared to age-matched control mice. It also stimulated neurogenesis increasing the number of newborn dentate granule neurons. The effect of andrographolide on APPswe/PS1ΔE9 transgenic mouse model of Alzheimer's disease showed an increased cell proliferation and density of immature neurons in the dentate gyrus. Concomitantly the increase in neurogenesis, also induced activation of the Wnt signaling pathway in the hippocampus of wild-type and APPswe/PS1ΔE9 mice, evident by increased levels of β-catenin, the inactive form of GSK-3β, and NeuroD1, a Wnt target gene involved in neurogenesis.<sup>32</sup>

## Antioxidant activity

Protective effect of andrographolide against H<sub>2</sub>O<sub>2</sub> induced cell death, reactive oxygen species, and lipid peroxidation was observed in HepG2 cells. It was found that andrographolide leads to activation of p38 MAP kinase, via adenosine A2A receptor signaling, which resulted in enhanced expression of Nrf-2, its translocation to nucleus

and activation of HO-1. Andrographolide also activated adenylate cyclase resulting in cAMP formation which in turn activated protein kinase A and inhibited GSK-3 $\beta$  by phosphorylation. Inactivated GSK-3 $\beta$  led to retention of Nrf-2 in the nucleus resulting in sustained expression of HO-1 by binding to its antioxidant response element (ARE).<sup>33</sup>



**Figure 3** Anticancer mechanisms of andrographolide.

\*mitogen activated protein kinase

\*\*endoplasmic reticulum

## Anticancer activity

The anticancer activity of andrographolide has been demonstrated in several types of cancers (Figure 3). Andrographolide inhibited invasive ability of A549 cells through down-regulation of PI3K/Akt signaling and inactivation of c-Jun/c-Fos followed by a reduction in MMP-7 expression.<sup>35</sup> It also enhanced chemosensitivity of tumor cells to doxorubicin through inhibition of STAT3 activity, which suggested a potential therapeutic strategy using andrographolide in combination with conventional chemotherapeutic agents for treatment of cancer.<sup>34</sup> Andrographolide induced cell cycle arrest<sup>35</sup> and triggered apoptosis in human cancer cells. Andrographolide also inhibited DU145 cell growth *in vitro* and *in vivo* via suppression of the IL-6 signaling pathway.<sup>36</sup>

Andrographolide inhibited expression of androgen receptor (AR) and prostate cancer cell growth and induced apoptosis. Andrographolide downregulated the AR expression at both mRNA and protein levels, prevented its nuclear translocation, and inhibited transactivation of its target genes. It also prevented the binding of Hsp90 to AR, resulting in proteasome-mediated AR degradation. Furthermore, andrographolide decreased the expression of androgen target genes such as prostate-specific antigen (PSA) and inhibited castration-resistant C4-2 cell growth by reducing AR expression and activity.<sup>37</sup> The inhibition of hepatoma tumor growth induced by andrographolide (10mg/kg) was found in a xenograft mouse tumor model *in vivo*. The miRNA chip analysis showed an increased expression of 22 miRNAs, whereas the expression of other 10 miRNAs decreased after treatment. Functional annotation of the target genes based on the differentially expressed miRNAs suggested that the majority of the genes were involved in a variety of signaling pathways, including miRNAs in cancer, mitogen-activated protein kinases (MAPKs) focal adhesion.<sup>38</sup> Yang et al.<sup>39</sup> studied the cytotoxic effect of andrographolide on human T-ALL (T-cell acute lymphoblastic leukemia) cells. It was found that 10 $\mu$ g/mL compound could significantly induce Jurkat cells' apoptosis, depending on the inhibition of PI3K/AKT pathway. Synergistic

anticancer effects of andrographolide and paclitaxel (PTX) (widely used in chemotherapy for cancer treatment) were studied against A549 NSCLC (*non-small cell lung cancer*) cells. The study demonstrated the effects of 24-48h treatment with 0.48-60.75nM PTX and 5.10-328.0 $\mu$ M andrographolide on cell cycle and intracellular reactive oxygen species (ROS), cellular proliferation and apoptosis. The antitumor efficacy of 20mg/kg PTX with 100mg/kg andrographolide was studied in a xenograft murine model. The combination inhibited the growth of A549 transplanted tumors by 98%.<sup>40</sup> Andrographolide showed a time- and concentration- dependent inhibitory effect on highly proliferative MDA-MB-231 breast cancer cell proliferation, however, the treatment did not affect normal breast epithelial cells, MCF-10A (>80 %). Increased production of reactive oxygen species (ROS) with a corresponding decrease in mitochondrial membrane potential (MMP), externalization of phosphatidylserine was observed, while the population of apoptotic cells increased with prolonged exposure to andrographolide. Additionally, caspase-3 and caspase-9 were activated while Bax and Apaf-1 expression were significantly increased with a corresponding decrease in Bcl-2 and Bcl-xL expression in andrographolide-treated cells.<sup>41</sup> Furthermore, andrographolide was also reported to inhibit prostate cancer cells (LNCaP, C4-2b, and PC), by targeting cell cycle regulators, CXCR3 and CXCR7 chemokine receptors.<sup>42</sup> 14-Deoxy-11,12-didehydroandrographolide (14-DDA), a major diterpenoid of AP, induced the formation of endoplasmic reticulum (ER) vacuoles and autophagosomes, with concurrent upregulation of LC3-II in the breast carcinoma cells. The mechanism of action involved increase in cytosolic calcium concentration leading to a collapse in mitochondrial membrane potential in LC3-II cells. The ER stress pathway, was significantly upregulated, DDIT3 knockdown suppressed the formation of both ER vacuoles and autophagosomes, indicating that 14-DDA-induced ER stress and autophagy is dependent on this transcription factor.<sup>43</sup> The inhibitory effects of andrographolide on the growth of multiple myelomas (MM) cells and its possible impact on the nuclear factor (NF)- $\kappa$ B signaling pathway were studied by Gao and Wang.<sup>44</sup> Andrographolide reduced the proliferation and

enhanced cellular apoptosis, caspase-9/3 activation of MM cells, and downregulated the expression of TLR4 and NF- $\kappa$ B protein. Further, andrographolide showed anticancer activity on various cancer cells, i.e CNS (U251), melanoma (M14), breast (NCI/ADR-RES), colon (SW620), prostate (DU145), and lung (H522).<sup>45</sup> *In vitro* and *in vivo* studies on colorectal cancer indicated that andrographolide treatment significantly re-sensitized HCT116/5-FUR cells (HCT116 cells which are 5-FU resistant) to cytotoxicity of fluorouracil (5-FU). Mechanism analysis showed that Andrographolide/5-FU co-treatment enhanced apoptosis level of HCT116/5-FUR cells and increased level of BAX. The study demonstrated that Andrographolide could directly target to BAX (Biotin-Andrographolide pull-down and cellular thermal shift assay), and Andrographolide-BAX interaction prevented BAX degradation and enhanced mitochondria-mediated apoptosis.<sup>46</sup> In another study andrographolide induced caspase-3 activation of HSC-2 oral squamous carcinoma cells.<sup>47</sup>

### Immunomodulatory activity

Andrographolide, 14-deoxy-11, 12-didehydroandrographolide and 14-deoxyandrographolide isolated from dichloromethane fraction of methanol extract of aerial part of AP, increased proliferation of human peripheral blood lymphocytes (HPBL) by 14, 5 and 7%, respectively, at 1 $\mu$ M concentration. All the three compounds enhanced the IL-2 induction in HPBLs. While andrographolide showed greater induction of IL-2, it was cytotoxic towards HPBLs at higher concentration.<sup>48</sup>

### Antimicrobial activity

A synergistic combination of andrographolide and arabinogalactan proteins showed antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*.<sup>49</sup> Another major phytoconstituent of AP, 14-Deoxy-11,12-didehydroandrographolide effectively reduced the mortality and weight loss of mice lethally challenged with A/chicken/Hubei/327/2004 (H5N1) or A/PR/8/34 (H1N1) influenza A viruses (IAV). Diterpenoid lactone, 3,19-isopropylideneandrographolide from AP, inhibited the herpes simplex virus type 1 (HSV-1) infection at the post-entry step.<sup>50</sup>

### Hepatoprotective

Chen et al.<sup>51</sup> investigated the modulatory potency of andrographolide on the expression and activity of cytochrome P450 (CYP) isozymes, glutathione S-transferases (GST), uridine diphosphate glucuronosyl transferases (UGT), and P-glycoprotein in rat liver. The effects of andrographolide on tolbutamide pharmacokinetics in rats and on the hypoglycemic effect of tolbutamide in high-fat-diet-induced obese mice were also investigated. Rats were intra-gastrically dosed with 2g/kg/day extract or 50mg/kg/day andrographolide for 5 days before administering a dose of 20mg/kg tolbutamide. AP ethanol extract and andrographolide reduced the AUC<sub>0–12h</sub> (area under the plasma tolbutamide concentration versus time curve) of tolbutamide by 37% and 18%, respectively, compared to control. AP ethanol extract and andrographolide accelerated the metabolism rate of tolbutamide through increased expression and activity of drug-metabolizing enzymes without impairing the hypoglycemic effect of tolbutamide. Andrographolide was found to protect liver cells from H<sub>2</sub>O<sub>2</sub> induced cell death by upregulation of Nrf-2/HO-1 mediated via adenosine A<sub>2a</sub> receptor signalling.<sup>51</sup>

### Conclusion

Plant derived natural compounds like andrographolide can be a cure-all for various medical problems. However, low andrographolides

content becomes a limiting factor for its otherwise huge market potential. The increase in the andrographolide content of AP still needs to be handled using more economical methods. Rhizosphere microbe interventions can offer an economical solution.

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### Conflict of interest

The authors have no conflict of interest.

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