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Original Article

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An Updated Review (Phytochemistry, Antimicrobial Pharmacology) on Indigenous King of Bitter (*Andrographis Paniculata*)

Navneet Kumar Verma[*1], Prashant Singh[2], Sushil Kumar Tiwari[1], Shiwani Jaiswal[1], Karunakar Prasad Dwivedi[1], Vinay Kumar[3], Shreya Maddheshiya[3]

[1] Associate Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209
[2] Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209
[3] Assistant Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209

ABSTRACT

Andrographis paniculata (King of Bitters), also known as Kalmegh, is a member of the Acanthaceae family. Andrographis paniculata is widely cultivated, and its relevance as a medicinal plant is expanding as evidence of its several therapeutic applications grows. Considering the plant's beneficial properties, it might be recommended as a safe and vital medicinal herb for mankind. This herb is rich in chemical components, including lactones, diterpenoids, diterpene glycosides, flavonoids, and flavonoid glycosides. It possesses numerous pharmacological effects, including antibacterial, hepatoprotective, anti-cancer, anticancer, hypoglycemic, immunomodulatory, and hypotensive action. The goal of this study is to conduct a literature review on Andrographis paniculata, specifically papers on therapeutic advantages, chemical features, and pharmacological evaluation. It is widely utilised as a home cure for numerous maladies in the Bangladeshi traditional system of medicine. Steroids, phenols, terpenoids, alkaloids, saponins, and flavonoids were the active chemicals found in Andrographis paniculata. The presence of active components, andrographolide and neoandrographolide, which are diterpenoids derivatives, contributes to the therapeutic potential of this plant.

Key Words: *Andrographis paniculata, Kalmegh, Andrographolide, King of Bitters.*

***Corresponding Author**
Navneet Kumar Verma
Associate Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209

INTRODUCTION

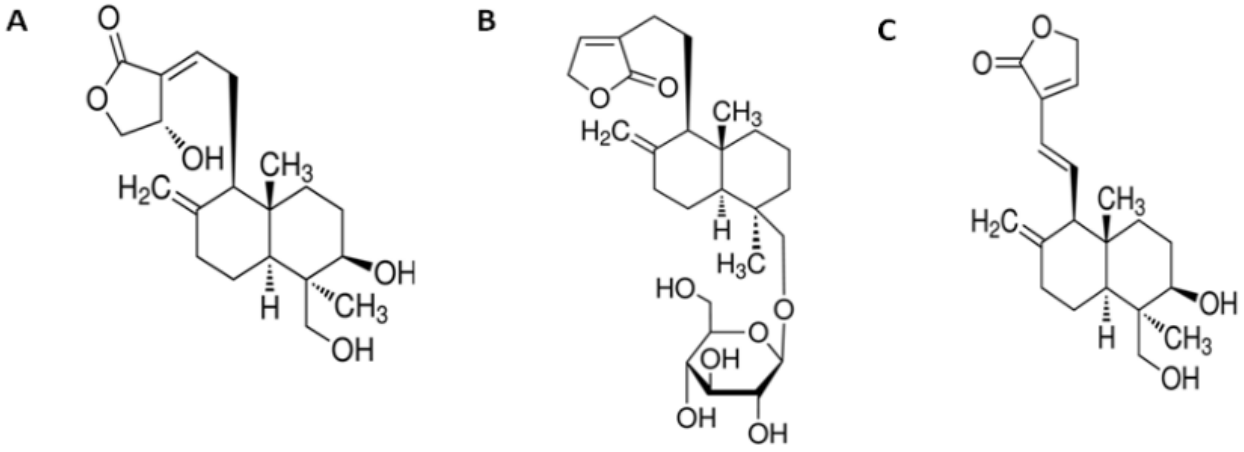
Andrographis paniculata is a branching annual with lanceolate green leaves that grows to a height of 60-70 cm [1]. 2. It thrives in Asian countries such as India, Sri Lanka, Pakistan, Java, Malaysia, and Indonesia. It is generally known as Kalmegh in India and is primarily found in the country's plains. It is one of the most commonly used medicinal plants in Ayurvedic and Unani systems of medicine. The plant is sometimes referred to as the 'King of Bitters' [2-3].

Because it has an exceptionally bitter taste in all parts of the plant. According to a literature review, the aerial portions of plants (leaves and stems) are most typically employed to extract active phytochemicals; however, the whole plant or 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.

Figure.1; *Andrographis paniculata* Plant

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, soandrographolide 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-Dglucopyranosyl- 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-dimethoxyxanthoneand 3,7,8-trimethoxy-1-hydroxyxanthone from the roots [5].



Andrographolide Neoandrographolide 14-Deoxy-11,12didehydroandrographolide

Furthermore, antibiotics usage causes some common side effects, including hypersensitivity and depletion of beneficial gut microorganism [6,7]. Acute upper respiratory tract infections (URTIs) is another significant cause of antibiotic resistance since physicians needlessly write antibiotic prescriptions [8–12]. Even though the vast majority of URTIs are mild, self-diagnosed and self-treated, they are the most common reason for absenteeism from school or work [13]. URTIs can be mainly caused by viruses, such as a rhinovirus, influenza virus, adenovirus, enterovirus, and respiratory syncytial virus. Bacteria like S. pyogenes, a Group A Streptococcus, may cause roughly 15% of sudden onset pharyngitis presentations [8]. Viral pharyngitis is mainly treated based on the symptoms that appeared, whereas bacterial pharyngitis can be treated with antibiotics. However, current evidence does not support the usefulness of antibiotics treatment in non-specific URTIs [13,14]. Therefore, research is urgently required to find alternatives to conventional medications for eradicating IDs. Natural products based therapy could be an excellent source of antimicrobial agents that would offer symptomatic relief since they have the high potentiality to inhibit the growth of microbes in the host-defence mechanism [4], as well as they offer promising outcomes in the scientific investigations [15–20]. Additionally, it would reduce unnecessary antibiotic prescription; therefore, the chances of antibiotic-resistance would be reduced. Nowadays, the philosophy of drug discovery has transformed into “one drug, multitarget” from “one drug, one target” [16,21–28]. Plant-derived secondary metabolites hold the potential of multi-targeting properties as they need to undergo evolving defence mechanisms of the plant against predators like bacteria, fungi, virus, even insects and herbivores [15,16,21,22,29,30]. A majority of the world population relies on medicinal plants for first-line treatment due to the severe side effects of synthetic drugs [31]. Moreover, plants’ ability to cure diseases and the necessity of their study in sacred texts motivated people to use natural remedies and researchers to study their pharmacology [32,33]. Plant-based secondary metabolites commonly isolated are phenols, tannins, flavonoids, lignans, terpenes, and a wide range of alkaloids [21]. Since natural products are better models with ideal pharmacokinetics/ pharmacodynamics properties [16], often feature biologically relevant molecular scaffolds and pharmacophore patterns that have evolved as preferred ligand-protein binding motif [22], they gained tremendous importance for the development of polypharmacological drugs for IDs, cancers, and neurological disorders [22,34]. Furthermore, about 80% of drugs are either natural products or analogues mimicking them, and steadily increasing approval rate (after the 1990s, the average annual approval rate is 10.3) of natural product-derived drugs from the US Food and Drug Administration (FDA) have encouraged researchers and pharmaceutical industries to search the effective multitarget drugs for various ailments [30,34]. Currently, a number of natural products, including morphine, quinine, reserpine, cocaine, and ephedrine, are now available in pure form as drug substances [15]. Besides, many pure compounds are identified by pharmaceutical scientists worldwide because of having advanced technology that eases and fasten the characterization and structural elucidation of isolated metabolites. Capitalizing on these findings are crucial for medical advancement to overcome unavoidable circumstances happed by

synthetic drugs. One attractive medicinal plant and its metabolites that have gained considerable and progressive interest for decades are Andrographis paniculata (Burm. f.) Wall. ex Nees. This annual plant belongs to the Acanthaceae family and is commonly known as ”King of thebitters” or ”Kalmegh”. It is native to India and Sri Lanka and widely found in Southern and Southeastern Asia, including Bangladesh, China, Hong Kong, Indonesia, Malaysia, Myanmar, Philippines, and Thailand [35–39]. Usually, the aerial parts, roots or leaves of A. paniculata are used separately. These plant parts are used traditionally as powder, infusion, or decoction form either alone or in combination with other medicinal plants for the treatment of leprosy, gonorrhoea, respiratory tract infections, scabies, boils, skin eruptions, chronic and seasonal fevers, griping, irregular bowel habits, loss of appetite, alopecia, general debility, diabetes, jaundice, dyspepsia, hemopathy, cough, oedema, liver complaints, dysentery, malaria, enteritis, helminthiasis, herpes, peptic ulcer, skin infections (topical use), and snake-bites (topical use) [35,36,39,40]. Modern science is focusing on validating the traditional claims of this plant through systemic investigations. Different extracts (i.e., acetone, chloroform, ethanol, hexane, methanolic or aqueous extract) and isolated pure metabolites from A. paniculata have been investigated for pharmacological properties, for example, antibacterial, antiviral, antifungal, antiparasitic, choleretic, hypocholesterolemia, anti-inflammatory, anti-hyperglycemic, hepatoprotective, anticancer, immunomodulatory, cardiovascular, antihyperlipidemic, emollient, anti-snake venom, anti-platelet aggregation, anti-fertility, carminative, and antipyretic properties at in vitro and in vivo conditions [41–53]. Clinical trials were conducted to validate the in vitro and preclinical antimicrobial pharmacology of A. paniculata. Several clinical trials have justified the anti-infectious activity of A. paniculata against URTIs, influenza, and HIV as well as its effectiveness in treating osteoarthritis and multiple sclerosis [54–59]. The clinical studies conducted using the standardized A. paniculata extracts alone or in combination with other medicinal plants (i.e., Kan Jang, Kalm Cold™). The extracts reported having approximately 4–6% of andrographolide [56,60], responsible for the beneficial effects of the plant extracts. In recent years, there are few more clinical studies conducted [12,61–73]. However, to date, Andrographolide or A. paniculata extracts have not achieved the human clinical trial stage. This might be because of low bioavailability that is attributed to the fast biotransformation and removal from the body [74] or due to a lack of a well-defined mechanism of action because it is considered as a highly promiscuous compound and engaged in covalent interactions with numerous previously unknown cellular targets in cell type-specific manner [75]. There are two important and typical challenges: (i) poor pharmacokinetics and (ii) limited bioavailability are involved with many natural products, for example, sitosterol, quercetin, genistein, rutin etc., prevent their in vitro to preclinical or clinical translation [76]. Nevertheless, there is a numerous investigation reported to have potential efficacy of A. paniculata for IDs as well as other ailments, including clinical efficacy. So, would A. paniculata extracts and their metabolites be a choice of better therapeutics? Would it be undergone for clinical development? Hence, there is a need to explore further the feasibility of A. paniculata with potential use as anti-infective agents for a wide range of invasive microbes. A better understanding of the mode of actions of the active ingredients of A. paniculata would enhance the clinical development of this drug. Additionally, there were several recent in vitro, in vivo, and a few clinical trials reported its potential therapeutic efficacy for antimicrobial pharmacology. To our best knowledge, critical evaluation of A. paniculata’s purported benefits is not substantial yet; hence, it would be important to review them before conducting further research in this area.

PHARMACOLOGICAL ACTIVITIES:

The usage of various sections of A. paniculata in folk medicine prompted scientists to investigate its pharmacological properties in order to validate this plant as a medicinal agent. Many studies have shown that this plant has antimicrobial, cytotoxic, antiprotozoan, antiinflammatory, antioxidant, immunostimulant, antidiabetic, antiinfective, hepatorenal protective, sex hormone modulatory, liver enzymes modulatory, insecticidal, neuroprotective, anticancer, antipyretic, antiplatelet, and toxicity properties [77-79].

Anti-microbial activity:

Aqueous extract, andrographolide and arabinogalactan proteins that were isolated from the dried herb of *A. paniculata* were screened for anti-microbial activity. The results showed that aqueous extract and arabinogalactan proteins possess antibacterial activity against *Bacillus subtilis* (*B. subtilis*), *Escherichia coli* (*E.coli*), *Pseudomonas aeruginosa* while andrographolide was the only one which is active against *B. subtilis*. All three were also reported to possess antifungal activity against *Candida albicans* [77]. The five rare noriridoides, andrographidoides (A-E) were screened for their anti-bacterial activity against *E. coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* and *B. subtilis*. None of the compounds showed inhibitory activity (MIC>100 μg/mL). Gentamycin, chloramphenicol and ciprofloxacin were used as positive controls [80].

Anti-inflammatory/Anti-allergic activity:

Aqueous extract when combined with methanol leaves extract showed significant alleviation of lipopolysaccharides that induced release of pro-inflammatory (NO, IL-1 β and IL-6), inflammatory (PGE2 and TXB2) and allergic mediators (LTB4). No inhibition was observed against histamine release (Chandrasekaran *et al*. 2010). Seven photochemicals, namely, andrographolide, neoandrographolide, isoandrographolide, andrograpanin, 7-O-methylwogonin, 14-deoxy-11,12- didehydroandrographolide and skullcapflavone (Figure 1) isolated from *A. paniculata* leaves were screened for *in vitro* anti-inflammatory and anti-allergic potential. The results showed that andrographolide, isoandrographolide, 7-Omethylwogonin and skullcapflavone-1 significantly inhibited inflammatorymediators NO and PGE2 release from

lipopolysacharide (LPS) stimulated cultured macrophages. However, IL-1β production in LPS stimulated macrophages was inhibited by andrographolide, isoandrographolide and 7-O-methylwogonin. Also, IL-6 production from LPS induced macrophages was significantly (P<0.01) inhibited by andrographolide, isoandrographolide and skullcapflavone-1 in a concentration dependent manner. The results also showed that andrographolide, isoandrographolide and skullcapflavone-1 significantly suppressed TXB4 released in A23187 activated HL-60 promyelocytic leukemia cells. Furthermore, the anti-allergic properties of the phytoconstituents was investigated on A23187 induced LTB4 production. The result showed 30.5% and 19.6% inhibition of LTB4 production in A23187 induced HL-60 promyeolocytic leukemia cells at concentrations of 63 μM and 33.5 μM for skullcapflavone and 7-O-methylwogonin respectively. The IC50 value for the reference standard captopril was 48 μmol/L. 7-O-methylwogonin was the only phytoconstituent that potently inhibited A23187 induced histamine release in RBL-2H3 rat basophil leukemic cells in a dose dependent manner[46]. Andrographolide, dehydroandrographolide and neoandrographolide isolated from the aerial parts of *A. paniculata* exhibited anti-inflammatory effects by interfering with COX enzyme activity. Andrographolide (30.1 μM) and dehydroandrographolide (28.5 μM) markedly inhibited COX-1 in ionophore A23187-induced human platelets. Dehydroandrographolide (28.5 μmol/L) and neoandrographolide (20.8 μM) strongly suppressed the LPS-stimulated COX-2 activity in human blood. In addition, dehydroandrographolide modulated the level of LPS-induced TNF-α, IL-6, IL-1β, and IL-10 secretion in human blood in a concentration dependent manner, showing that dehydroandrographolide has the highest efficacy. The result further showed that the mechanism of dehydroandrographolide may be related to down-expression of genes involved in the inflammatory cascade [81].

Andrograpanin (15-90 μM) isolated from the ethanol extract of the leaves inhibited NO and pro-inflammatory cytokines (TNFα, IL-6, IL-12p70) in a dose dependent manner from lipopolysaccharide activated macrophages. Significant (P<0.05) inhibition of NO was evident at a concentration of 30 μmol/L and at a concentration of 75 μM. Andrograpanin almost completely inhibited NO production. Significant inhibition of pro-inflammatory cytokines was evident at a concentration of 1.5μmol/L and there was an almost complete inhibition at a concentration of 90μmol/L. The RT-PCR and western blotting assays showed that andrograpanin inhibited productions of NO and pro-inflammatory cytokines through down-regulating iNOS and pro-inflammatory cytokines gene expression levels as well as p38 mitogen activator kinase signaling pathways. Further study showed that andrograpanin has more ability of down regulating IL-12 p35 and p40 proteins than their mRNA levels. This suggests that andrograpanin might be involved in down regulating the post-translation of IL-12 p35 and 40 proteins [82].

Antioxidant activity:

Andrographolide and aqueous extract of *A. paniculata* were screened for their antioxidant activity on nicotine induced oxidative stress in liver, kidney, heart, lungs and spleen of male wistar rats. The results showed that intraperitoneal administration of *A. paniculata* (25 mg/kg) and *Aphanamixis polystachya* (25 mg/kg) for a period of 7 days significantly (P<0.05) reduce levels of lipid peroxidation and increase antioxidant enzymes status in five organs screened as compared to nicotine [83]. The methanolic and aqueous leaves extracts of *A. paniculata*, andrographolide and 14-deoxy-11, 12-didehydroandrographolide exhibited lipid peroxidation inhibition in Sragues Dawley rats and free radical scavenging activity against Diphenyl picrylhydrazyl (DPPH). The lipid peroxidation inhibition activity varied from 55.6% to 63.9% and 33.78% to 33.77% for methanolic and water extracts respectively. The activity of the methanolic extracts were higher and significantly different (P<0.05) from that of the water extract. The methanolic extract exhibited free radical scavenging activity ranging from 45.67% to 53.82%. The activity of andrographolide was 40.2% and for 12-didehydroandrographolide it was 46.43%. The water extract exhibited poor free radical scavenging activity ranging from 25.29% to 28.77%. The methanolic, water extracts and isolated compounds exhibited a lower free radical scavenging activity as compared to quercetin (89%) and butylated hydroxylanisole (71%) used as positive controls [84]. A fourteen-day oral treatment of Sprague Dawley rats with methanolic extract (1g/kg body weight) of dried leaves followed by carbon tetrachloride (CCl4) challenge preserved antioxidant enzyme-catalase and superoxide dismutase activities in erythrocytes. Whereas, lipid peroxidation, alanine transaminase, aspartate transaminase and plasma thiobarbituric acid reactive substances were restored to values as compared to that who did not receive CCl4. Andrographolide, 14-deoxy-11, 12- didehydroandrographolide were traceable in rat plasma followed by an oral dose of methanolic dried leaves extract (1 g/kg body weight) suggesting that these diterpenes may be responsible for the observed antioxidant activity [85].

Antiprotozoan activity:

Four xanthones were isolated from root fractions and screened for antiplasmodial activity against *Plasmodium falciparum*. Only a compound 1,2-dihydroxy-6,8-dimethoxyxantone possessed substantial antiplasmodial activity against *Plasmodium falciparum* with an IC50 value of 4μg/ ml. This compound also exhibited *in vivo* antimalarial activity in mice infected with *Plasmodium berghei* where it produced substantial reduction (62%) in parasitemia [42]. This study involved the root fractions that showed higher antimalarial activity ascompared to a previous study of fractions isolated from the leaves [86]. Andrographolide, neoandrographolide, deoxyandrographolide and andrographoside isolated from the leaves have been shown to possess some activity against *Plasmodium berghei* NK65 in *Mastomys natalensis* [87].

Insecticidal activity:

The ovicidal and larvicidal activity of the crude leaves extract of *A. paniculata* with five different solvents like benzene, hexane, ethylacetate, methanol and chloroform were tested against early third instar larvae of *Culex quinquefasciatus* (Say) and *Aedes aegypti* (Linn). The benzene, hexane, ethylacetate, methanol and chloroform extracts were found to be more effective against *Culex quinquefasciatus* than *Aedes aegypti*. The LC50 values were 112.19, 137.48, 118.67, 102.05, 91.20 mg/L and 119.58, 146.34, 124.24, 110.12, 99.54 mg/L respectively. The methanol and ethyl acetate extracts were found to be most effective for ovicidal activity against the two mosquito species. The extract of methanol and ethylacetate also exerted 100% mortality at a concentration of 200mg/L against *Culex quinquefasciatus* and at 250 mg/L against *Aedes aegypti* [88].

Antiinfective activity:

The efficacy of the leaves extract of *A. paniculata* in the treatment of symptoms of uncomplicated upper respiratory tract infection has been reported. The findings obtained in a randomized double blind placebo controlled clinical evaluation using the visual analogue scale for quantification of symptoms. It showed that the Kalmcold treatment significantly ($P<0.05$) decreased all the symptoms score except for earache whereas symptoms remained unchanged or got worse after Day 3 for the placebo group. The study revealed that Kalmcold was 2.1 times or 52.7% more effective than placebo in reducing symptoms of uncomplicated upper respiratory tract infection [89]. *A. paniculata* extract SHA-10 (1200 mg/day) administered for a period of five days. It significantly ($P<0.05$) reduced the intensity of the symptoms (tiredness, sleeplessness, sore throat and nasal secretion) in uncomplicated common cold at the beginning of Day 2 treatment over placebo group. On Day 4, a significant decrease in the intensity of all the symptoms (headache, tiredness, ear ache, sleeplessness, sore throat, nasal secretion, phlegm, frequency and intensity of cough) was observed for *A. paniculata* group [90].

Liver enzyme modulation:

Both andrographolide and 14-deoxy-11,12- didehydroandrographolide inhibited mRNA and protein expression of CYP1A2, CYP2D6, and CYP3A4 in HepG2 hepatoma cells. The lowest concentration (0.3 μm) of both diterpenoids produced more than 50% reduction in mRNA and protein expression of CYP3A4. This reduction was consistent with the enzyme activity. Both the compounds also reduced the ability of dexamethasone to induce CYP3A4 expression [91]. Andrographolide induced enhanced expression of CYP1 in PAH-responsive C57BL/6 male mice and did not alter CYP1 expression in PAH non-responsive DBA/2 male mice, ovariectomized females and orchiectomized male mice. However, the treatment with testosterone restored the effect of andrographolide on CYP1 in both orchiectomized males and ovariectomized females. This observation suggested a role for a male hormone system as a crucial mediator of modulation of CYP1 expression by andrographolide [92]. Andrographolide and *A. paniculata* extract significantly ($P<0.05$) increased the clearance and reduced the area under concentration time curve of theophylline (1 mg/kg) in blood of male Sprague Dawley rats. The elimination half-life and mean residence time of theophylline were shortened by 14% and 17%, respectively in the andrographolide treated rat in the presence of high dose theophylline (5 mg/kg). However, theophylline (5 mg/kg) accumulated in the blood of rats was pretreated with *A. paniculata* extract. This suggested that some herbal constituents present in *A. paniculata* extract may interact with theophylline and retard its elimination when administered at a high dose [93].

Sex hormone/function modulation:

Oral administration of the leaves extract in doses of 200, 600 and 2000 mg/kg body weight (i.e. 30, 90 and 300 fold higher than its daily therapeutic dose in humans) to pregnant rats for a period of 19 days for 200 mg/kg group and 11 days for 600 and 2000 mg/kg group respectively did not show any effect on the elevated levels of progesterone in the blood plasma of pregnant rats when compared with control groups. This suggests that *A. paniculata* at therapeutic doses cannot induce abortion [94]. Andrographolide (50 mg/ kg body weight) administered to male ICR mice significantly ($P<0.05$) decreased the mounting latency at 120 min and 180 min and increased the mounting frequency at 180 min after treatment. This suggested an improvement in sexual functions. The pre-incubation of endothelium-intact aortic strip with andrographolide for 10 min before adding nor-epinephrine resulted in a significant reduction in nor-epinephrine effect on aortic strip tension. An observation suggested that andrographolide improves sexual function by causing smooth muscle relaxation and increasing blood flow to the penis. Also, daily treatment of male mice with andrographolide (50 mg/kg) for 2, 4, 6 or 8 weeks significantly ($P<0.05$) increased serum testosterone levels on week 4 and this level declined back to normal (pretreatment levels) on week 6 and 8 with continued treatment. Moreover, andrographolide (50 mg/kg) was shown to have no significant effect on sperm count and motility [95].

Toxicity:

The safety of *A. paniculata* extract (Kalmcold) in genotoxic tests has been reported. In a study, the LD50 values has been determined to be higher than 5g/kg rats body weight in an oral acute toxicity [96]. Testicular toxicity was assessed by reproductive organ weight, testicular histology and ultra-structural analysis of leydig cells. The testosterone levels were not found after 60 days treatment with ethanol extract of dried herbs of *A. paniculata* in Sprague Dawley rats at doses of 20, 200 and 1000 mg/kg which suggested the relative safe toxicity profile [97-98].

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 50 μM), 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 12.5 μM. 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 [99]. 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 24 h. HO-1 is a known gene target of transcription factor Nrf2, which is critically involved in cellular defense against oxidative stress [100]. 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 [101]. 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 [102].

Cytotoxic and anti-tumor Activity:

The inhibition of hepatoma tumor growth induced by andrographolide (10 mg/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) and focal adhesion [103]. Yang *et al* [104] studied the cytotoxic effect of andrographolide on human T-ALL (T-cell acute lymphoblastic leukemia) cells. It was found that 10 μg/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. 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 andApaf-1 expression was significantly increased with a corresponding decrease in Bcl-2 and Bcl-xL expression in andrographolide-treated cells [105]. 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 [106]. 14-Deoxy-11,12-didehydroandrographolide (14-DDA), a major diterpenoid of AP, induced the formation of endoplasmic reticulum (ER) vacuoles and autophagosomes, with concurrent up regulation 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 up regulated, 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 [107]. The inhibitory effects of andrographolide on the growth of multiple myelomas (MM) cells and its possible impact on the nuclear factor (NF)-κB signaling pathway were studied by Gao and Wang [108].

Antipyretic activity:

Antipyretic, analgesic properties of nilavembu kudineer chooranam: a classical preparation used in the treatment of chikungunya fever was reported by Anbarasu, et al [109]. Madav, et al [110] 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 Brewer's yeast-induced pyrexia in rats and significant ($p < 0.05$) anti-ulcerogenic activity in aspirin induced ulceration in rats.

Antiplatelet activity:

Phytoconstituents and extracts of *Andrographis paniculata* was reported to exhibit anti-platelet activity by various mechanism of actions viz. decreasing platelet activating factor [111] and increasing eNOS-NO/cyclic-GMP pathway by decreasing PLC2-PKC and PI3 kinase/Akt-MAPKs [112]. Inhibitory effect of *Andrographis paniculata* extract and its

active diterpenoids on platelet aggregation was studied by Thisoda, et al [113]. 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 [114] 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 [115] isolated two new flavones designated as andropaniculosin A and ropaniculoside A and 30 known compounds from the whole plants of *Andrographis paniculata*.

Adverse effects:

An overdose of *Andrographis paniculata* extracts caused vomiting, gastric discomfort and loss of appetite that may be due to very high bitter taste of the herb [116]. 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 [117].

CONCLUSION

Andrographis paniculata has been used to cure a variety of disorders, including liver damage, infection, hyperglycemia, cancer, and other ailments. Andrographolide is a diterpenoid lactone with a variety of pharmacological properties as defined by indigenous medicine. In addition to its many medicinal use, andrographolide has some adverse effects such as nausea, vomiting, and loss of appetite that can only be detected when overdose. As a result, researchers may go on to build potent formulations containing Andrographis paniculata and its isolated molecule, andrographolide, using herbal drug delivery vehicles. For a variety of causes, human invading microorganisms are becoming resistant to available medicines. Because A. paniculata acts on immunological modulation, medication resistance is less likely to occur. Even though A. paniculata has potential antibacterial activity, more research on the method of action, impact of available antimicrobial drugs, and specific administration route and schedule is needed. The active ingredients of A. paniculata could be a source of antibacterial agents, and investigating their therapeutic potential based on clinical implications is worthwhile. We have investigated significant antimicrobial compounds in A. paniculata, but little is known about their molecular pathways in response to bacteria or host-infected cells. Human-invading germs are growing resistant to existing medications due to a variety of factors. Medication resistance is less likely since A. paniculata works on immunological regulation. Despite the fact that A. paniculata has potential antibacterial activity, more research on the mechanism of action, the impact of current antimicrobial medicines, and the specific administration route and schedule is required. The active components of A. paniculata could be a source of antibacterial agents, and it is worthwhile to investigate their therapeutic potential based on clinical implications. We found antimicrobial chemicals in A. paniculata, but little is known about their molecular processes in response to bacteria or host-infected cells. If we consider the overall efficacy of A. paniculata treatment, it would be a worthy consideration as a natural product treatment option for acute URTIs as currently, there is a lack of compelling therapeutic opportunity for IDs.

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