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Review Article

A COMPREHENSIVE REVIEW OF KALMEGH'S BIOLOGICAL ACTIVITIES (*ANDROGRAPHIS PANICULATA*)

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ABSTRACT

Kalmegh is a valuable herb belonging to the family Acanthaceae that has been used traditionally in India and Southeast Asia to cure a variety of illnesses like diabetes, viral hepatitis, high blood pressure, ulcers, and malaria. It has many important bioactive compounds, such as diterpenoids, flavonoids, and polyphenols. The most common and abundant diterpenoid is andrographolide. It cures and prevents several diseases in humans. Andrographis and its extract have been documented for their various medicinal uses. A full bibliographic inquiry was conducted using extensively used scientific databases like Web of Science, research articles, and online as well as offline sources. A goal of the current review is to analyze the *Andrographis paniculata*'s traditional usage, chemical components, and biological activities to highlight, explore, and lay the groundwork for future research.

Keywords: *Andrographis paniculata*, Bioactive constituents, Pharmacology, Medicinal uses hepatoprotective, Antioxidant activity

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INTRODUCTION

Medicinal plants have been integral to man's health and healing since the dawn of human civilization. Despite of significant advancements made in allopathic medicines during the 20th century, both the ancient and contemporary systems of medicine continue to rely heavily on plants as a source of medications. The majority of the world's populations, who reside in underdeveloped nations, rely on traditional medicine and herbal remedies to meet their primary healthcare needs. According to reports, up to 8000 plants can be used in the Ayurvedic, Homeopathic, Siddha, Unani, and Tibetan medical systems [1-3]. One of them is *Andrographis paniculata* commonly known as 'King of Bitter'. It generally grows abundantly in Southeast Asia, Sri Lanka, and India. It can increase in height to a maximum of one meter, with small, hairy white to pink blooms and lanceolate leaves. The leaf is the primary therapeutic component, while the entire plant, including the root, is used for a variety of illnesses. In India, it grows in the rainy season, when heat and humidity with lots of sunshine are the ideal climate conditions for the plant.

In India, both tribal and traditional medicine systems make considerable use of *Andrographis paniculata* as a home treatment for various illnesses. The most utilized component of *Andrographis paniculata* is the aerial part, and its major bioactive constituents are diterpenoids, flavonoids, and xanthones. In Asia and Europe, whole plants and leaves are utilized as folk remedies for a variety of illnesses. This plant is prescribed to treat several chronic and infectious illnesses, such as sore throats, fever, herpes, and upper respiratory and gastrointestinal infections [4–7].

Ethnobotanical uses

For ages, Asia's traditional healers have used the leaves and roots of *Andrographis paniculata* to treat a variety of illnesses like fevers, diarrhea, and getting rid of intestinal worms [8]. The plant is used as a liver tonic, blood–purifier, and antidote for snake bites, scorpions, and centipede stings [9, 11]. It is also useful for burning sensations, wounds, skin diseases, and leprosy. Plant powder is used to relieve itching. Additionally, the juice and macerated leaves are utilized as a home cure for children's flatulence and diarrhea. They are converted into pills and suggested for infants suffering from colic and other gastrointestinal issues [8]. The tribal society used the herb as an astringent, anodyne, tonic, and alexipharmic agent. The leaves have been used in decoction or infusion with positive outcomes for scabies, fever, anemia, and a sluggish liver. The root's tincture is employed as a tonic, stimulant, and aperients. Various plant parts, either by themselves or in combination with other Indian plants, are used in many Indian and other Asian communities for neuralgia, fever recovery, and liver torpidity. The herb serves as the major constituent of a traditional home treatment that is employed as a febrifuge and bitter tonic [10].

Bioactive compounds of Andrographis

The aerial portions and roots of *Andrographis paniculata* contain a wide range of significant bioactive substances. Terpenoids, which make up a substantial amount of their constituents and medicinal capabilities, are the significant metabolites. The other components are flavonoids, polyphenols, xanthones, and macro-and trace elements.

Terpenoids

Diterpenoid lactones are the main terpenoid that are extracted from *Andrographis paniculata's* aerial parts and roots (table 2). The majority of the isolated and recognized diterpenoids from *Andrographis paniculata*, in terms of both quantity and occurrence, are andrographolide, deoxyandrographolide, and neoandrographolide [12]. Andrographolide is a white, crystalline substance with an extremely unpleasant taste. It has a variety of pharmacological characteristics and was initially extracted in pure form by Gorter in 1911. Andrographolide is an α-alkylidene γ-butyro-lactone molecule with three-OH groups at Carbon-3, 14, and 19 that is found primarily in leaves. Deoxyandrographolide and neoandrographolide are also dominant diterpenoids that are usually found in the aerial parts of plant. Several researchers have isolated these diterpenoids. Other diterpenes besides the prominent ones have also been discovered by several researchers, including a unique terpenoid (23-carbon) found in the plant's roots and aerial parts.

Flavonoids

Flavones are extracted from all parts of the herb (table 1). Flavones, such as 5, 7, 2, and 3'-tetra methoxy flavones, as well as 5-hydroxy-7, 2-, and 3-trimethoxyflavones, are found throughout the plant [22]. The root and aerial parts of the plant contain the flavone 7-O-methyl-dihydro wogonin, while the 1,2-methyl ether type of flavone is found in all portions of the plant. The flavonoids 5-hydroxy-7, 8, 2, and 5'-tetramethoxyflavone can be found throughout the entire plant. An instance of a flavone distributed throughout the entire plant is dihydroskullcapflavone [27, 28].

Table 1: Bioactive compounds of *Andrographis paniculata*

S. No.	Compounds	Basic structure type	Extracted from plant parts	Refer
1	Andrographolide	Diterpenoid lactone	Aerial plants	[12]
2	Deoxyandrographolide		parts	[13, 14]
3.	Neo-Andrographolide			[13, 14]
4.	Andrographolide D: (14-deoxy-11,12-didehydroAndrographolide)			[15]
5	Andrographolactone			[16]
6.	Andrographanin	Diterpene	Leaves	[31]
7.	Andrographoside	Diterpene	Leaves	[21]
8.	19-O-β-Dglucopyranosyl-entlabda-8(17) 13-diene-15,16,19-triol entlabdane	Ent-labdane diterpenoids	Aerial plants parts	[17-20]
9.	3-O-β-Dglucopyranosyl-14,19-dideoxy andrographolide			
10.	8-α-methoxy14-deoxy17β-hydroxy andrographolide entlabdane			
11.	5,7,2',3-tetramethoxy flavones.	Flavonone	All parts of a plant	[23]
12.	5-hydroxy-7,2',3'-trimethoxy flavones	Flavone	All parts of a plant	[23]
13.	7-O-methyl-dihydro wogonin			[24]
14.	Flavone-1,2'methylethe			[25, 26]
15.	5-hydroxy-7, 2', 3'-tri methoxyflavones	Flavonoids	All plant parts	[27, 28]
16	Dihydroskullcapflavone	Flavone	All plant parts	[27, 28]

Table 2: Other chemical constituents of *Andrographis paniculata*

S. No.	Chemical constituents	Extracted from a plant part	Refer.
1.	1,8-dihydroxy-3,7-dimethoxy-xanthone	Root of plant	[29]
2.	4,8-dihydroxy-2,7-dimethoxy-xanthone		
3.	1,2-dihydroxy-6,8-dimethoxy-xanthone		
4.	3,7,8-trimethoxy-1-hydroxy-xanthone		
5.	Andrographidoid A-E		[30]
6.	Curvifloruside		
7.	Arabinogalactan	Herbs	[32]

Other compounds

In addition, using chromatography, four distinct xanthones found in the roots of *Andrographis paniculata* have been extracted and identified (table 2). They were identified as 1, 8-dihydroxy-3,7-dimethoxy-xanthone, 4,8-dihydroxy-2,7-dimethoxy-xanthone, 1,2-dihydroxy-6,8-dimethoxyxanthone and 3,7,8-trimethoxy-1-hydroxy-xanthone [29]. The roots of *Andrographis paniculata* were used to isolate five unusual noriridoids, including andrographolide A-E and curvifloruside. By Prajjal and his associates in 2007, arabinogalactan proteins were extracted from the dried herbs [32], and microelements (K and Ca) and trace elements (Cr, Mn, Co, Ni, Zn, Cu, Se, Rb, Sr, and Pb) were discovered and measured in the roots.

Pharmacological properties of *Andrographis paniculata*

Scientists have explored *Andrographis paniculata's* pharmacological qualities to confirm its usage as a therapeutic agent in the therapy of many illnesses as a result of its use in folk medicine, particularly in Asia [33, 34]. Studies have revealed that this plant have variety of biological activities, including antioxidant activity [35, 36], anti-bacterial [37, 38], anti-viral [39], cold and fever [40], anticancer activity [41, 42], urinary tract infection [43], and anti-diabetic activity [44, 45], cardiovascular activity [46, 47], immunomodulatory activity [48, 49] and anti-hepatotoxic [50, 51], etc

Antioxidant activity

In many European states and Asia, Andrographis paniculata is used as a natural antioxidant. A study of Verma et al., observed that how Kelmegh's aqueous extract affected the hepatic defense system in AKR mice having lymphoma [52]. He also observed that taking an oral dose of a plant's aqueous extract considerably increased the activity rate of glutathione-s-transferase, catalase, and superoxide dismutase. Andrographolide significantly affected the hepatic antioxidant defense system and lipid oxidation in control mice, according to Das et al., [53]. Its hepato-protective reactivity against hexa-chloro cyclohexane was also tested for oxidative injury. He discovered that plant extract and active ingredient andrographolide exhibits a antiradical activities against several pathophysiological oxidants using liver sub-cellular organelles of rat as model systems [54]. When the plant's antioxidant and anti-inflammatory properties were investigated, it was discovered that the methanolic extract inhibits the production of free radicals such as superoxide, hydroxyl radicals and nitric oxide in vitro system [55]. The RAW cells stimulated with lipo-polysaccharide (LPS), andrographolide decrease nitric oxide formation and stabilize the inducible synthase protein [56, 57]. Neoandrographolide, which was an extract from the EtOAc portion of methanol extract, inhibits in vitro and ex vivo NO production in Bacillus Calmette-Guéin (BCG)-induced peritoneal macrophages in mice [58].

Antioxidants are essential for the cure or mitigation of a variety of illnesses. Numerous clinical problems, including degenerative diseases, have been linked to the patho-physiology of natural antioxidants. It might accelerate the ageing process and progressive impairment of the immune function [59]. Additionally, it has been suggested that the phenolic content of drugs and their antioxidant activity may be related. The flavonoids are a group of phenolic compounds with bioactive qualities, including the capacity to scavenge free radicals, inhibit hydrolytic and oxidative enzymes, and serve as an anti-inflammatory [60].

A number of diseases in the human body are caused by free radicals. It may be important to consume natural oxidants as free radical scavengers in order to enhance the compromised immune system [88]. According to reports, the antioxidant constituents of plant materials buffer the body from damage produced by free radical-induced oxidative stress and protect against cancer and coronary heart disease [84]. Positive results were obtained from studies on *Andrographis paniculata's* antioxidant activities in conjunction with the herb's diterpenoid components. There are; however, very few studies comparing the antioxidant properties of *Andrographis paniculata* to those of synthetic antioxidants.

Anti-microbial activity

Andrographis paniculata has been extensively used against the activity of various bacteria, viruses, and parasites. It was observed that ethanolic leaf extract decreased the growth of *E. coli* and *S. aureus in vitro*. *In vitro* development of *Proteus vulgaris* to be inhibited by a 50% methanol extract of *Andrographis paniculata*.

Another study revealed that significant anti-microbial activity was found with the aqueous extract of andrographolide and arabinogalactan proteins of *Andrographis paniculata* [32]. *Streptococcus mutant* and *S. mutans* adhesion are inhibited by plant ethanol extract at the necessary doses *in vitro* (0.5 percent). A study found that Andrographis water extract may have potential antibacterial effects on both strains of bacteria. According to Wiart *et al.*, *Andrographis paniculata* Nees' ent-labdane diterpenes reduced the propagation of the herpes virus and had no discernible lethal effects at viricidal concentrations [39, 61]. At 0.05 mg/ml concentration, the chloroform extract greatly slowed the growth of the malaria parasite within 24 h of incubation [62]. Asian societies have long relied on the leaves of *Andrographis paniculata* to reduce body temperatures and relieve fever. According to Misra *et al.*, a methanolic extract of kalmegh has antimalarial action against the malaria-causing organism *Plasmodium berghei* [63]. Studies of Andrographis conducted *in vitro* and vivo showed that it has anti-malarial capabilities that can be investigated further to produce potent anti-malarial drug in future [86].

Hepato-protective activity

In Indian medical systems, *Andrographis paniculata* is commonly utilised as a hepatostimulant and hepatoprotective. The hepatoprotective activity of *Andrographis paniculata* was reported by many groups of researchers. There is few research on the impact of *Andrographis paniculata* crude extracts on liver function. Andrographolide significantly increased choleretic effects on anaesthetized guinea pigs, according to Shukla *et al.* [64]. Andrographolide, a typical hepatoprotective drug, was found to be more effective (0.75–12 mg/kg) in a comparative analysis than silymarin [65]. According to reports, Andrographolide increases bile flow significantly in animals, making digestion easier. After a study of consumption of Andrographolides accumulation in different organs like the brain, spleen, heart, lung, kidney, liver, intestine, etc. Researchers discovered that both assimilation and removal were quick; 90% of the substance was eliminated through the renal and gastrointestinal tract within 48 h. They discovered that a plant might effectively heal hepatitis [66].

Anti-fertility

The use of *Andrographis paniculata* as natural medicine is increasing day by day; hence its adverse effects on the human body if any also is the topic of interest. In regard to this, *Andrographis paniculata's* potential impact on male and female reproduction has been studied. A study by Akbarsha *et al.*, reported that *Andrographis paniculata's* antispermatogenic and antiandrogenic effects were demonstrated in male *albino rats* fed 20 mg/day dose of 60 d in leaf powder form, it resulted in the loss of spermatogenesis, degeneration, alternations in the seminiferous tubules, sperm vesicle, ventral prostate gland, coagulating gland and regression of the Leydig cells [67]. According to research by Zoha *et al.*, female mice did not pregnant after taking 2 gm/kg weight per day for six weeks plant powder whereas 95.2% of female control mice did not receive *Andrographis paniculata* became pregnant. This suggests that the herb has a strong anti-fertility effect and should not be used while pregnant [68]. Similar effects were also seen in male *Wistar albino rats* after 48 d of oral administration of andrographolide. The dried extract of *Andrographis paniculata*, according to Burgos *et al.*, blocks voltage-sensitive calcium channels to cause uterine relaxation [43].

Anti-malarial activity, cold, and fever

For many years, Asian societies have utilized the leaves of *Andrographis paniculata* to treat fever and reduce body temperatures. According to Misra *et al.*, Kalmegh's methanolic extract exhibits anti-malarial efficacy against *Plasmodium berghei*, malaria-transmitting parasites [63]. The extract clearly demonstrates suppression of the parasite's ability to reproduce. It has also been found that the lactate dehydrogenase (LDH) assay can inhibit anti-malarial efficacy against *Plasmodium falciparum* [85]. Compounds 1, 2-dihydroxy-6, 8-dimethoxyxanthone, which has an IC_{50} value of 4 µg/ml, were found to have significant anti-plasmodial action against *Plasmodium falciparum in vitro* experiments. The most active xanthones were those with hydroxyl groups in the second position, while those with the hydroxyl group in the first, fourth, or eighth positions had very little activity [29].

Additionally, a pilot double-blind study on the use of the herbal treatment '*Kang Jang'* to prevent the common cold was reported (standardized to 4 percent Andrographolides). It was discovered that "*Kang Jang*" (doses of 200 mg daily) showed a 30% reduction in the incidence of cold [69]. The usage of *Andrographis paniculata* in the treatment and prevention of influenza and cold flu viruses has been recognized [70]. In a separate study, 152 adult patients with pharyngotonsillitis were examined, and after seven days, the patients were randomly assigned to receive either paracetamol or a 3 or 6 g daily dose of the herb [86, 87]. On day third, paracetamol or high-dose Andrographolide was significantly more effective than low-dose Andrographolide in reducing fever and sore throat. On day seven, the same clinical improvement was found [71].

Anti-HIV activity

When the anti-HIV properties of *Andrographis paniculata* were examined, it was discovered that andrographolide changes cellular signal transduction mechanisms to inhibit the spread of the virus and halt disease progression. The anti-HIV and cytotoxic effects of bis-andrographolide ether, andrographolide, 14-deoxy-11,12-didehydroandrographolide, andrograpanin, as well as 5-hydroxy-7,8-dimethoxyflavanone and 5-hydroxy-7,8-dimethoxyflavone, were investigated [72]. Clinical experiments conducted by Calabrese *et al.* showed anti-HIV effectiveness, Dehydro andrographolide succinic acid monoester (DASM) inhibits HIV *in vitro*. A doses between 1.6 and 3.1 mcg/ml, was not harmful to the H9 cell. Additionally, dehydroandrographolide succinic acid monoester inhibited two additional HIV-1 strains and one other HIV-2 strain [73]. For three weeks, 5, 10, and 20 mg/kg doses of andrographolide were given, and the lymphocyte level of HIV individuals significantly increased [74, 75].

Anti-venom activity

According to conventional medical practice, *Andrographis paniculata* is a natural remedy for snake bites. Mice poisoned with cobra venom were given an intraperitoneal injection of ethanolic extract from leaves (25 g/kg body weight), which significantly delayed respiratory failure and death. At 2 mg/ml, this extract also caused contractions in the guinea-pig ileum. These contractions were unaffected by antihistamines but were boosted by physostigmine and prevented by atropine. According to the study, the extracts' anti-venom properties may be explained by a large increase in muscarinic activity rather than by altering the activation of nicotinic receptors. In mice, *Andrographis paniculata* ethanolic extract showed some protective effects against red scorpion venom [76].

Anticancer activity

In numerous prostate cancer cell lines, andrographolide acts as a therapeutic agent. Andrographolide is quickly digested when used orally, unlike other cytotoxic anticancer medications. A 2-cell line panel made up of the colon (HCT-116) and breast (MCF-7) cancer cell lines showed antitumor activity as well [47]. In a study conducted by Singh using various cancer cell lines, they found that it has the potential to be chemoprotective against chemotoxicity, including carcinogenicity. In late-stage malignancies, where there is an increase in the cytotoxic activity of natural killer cells (NK) and tumor necrosis factor-alpha (TNF-alpha), they utilize this combination. Diterpenes, flavonoids, and stigmasterols are all present in the plant extract of *Andrographis paniculata*, with Andrographolide being the main active diterpenoid and having potent cytotoxic activity against human epidermoid cancer and the P388 mouse leukemic cell line [77, 86].

Antidiabetic activity

Oxidative stress and diabetes are closely connected diseases. As free radicals, oxygen plays a significant role in diabetes complications. According to a study on blood glucose, when an Ayurvedic formulation supplemented with this plant, i.e., IIogen-Excel, is taken orally for 60 d, total hemoglobin, hepatic glycogen, and plasma insulin levels all increase while blood glucose levels are markedly reduced [78]. Researchers studied how the plant influenced the

estrous cyclicity of rats that had been given alloxan to make them diabetic, and they found that Kalmegh has the ability to reverse the rats' abnormal estrous cycles. It was also reported that water extract (1 g/kg body weight) had a significant (P 0.001) hypoglycemic effect on experimental rabbits [79]. In a dose-dependent way, andrographolide oral therapy reduced the levels of plasma glucose in streptozotocin-induced diabetic rats

Cardiovascular activity

Numerous researchers have published independent reports on the cardiovascular activity of *A. paniculata* and its chemical components. Experimental animal's artery wall thickening was successfully prevented by the herb's extracts. The plant extract also has the additional benefit of triggering fibrinolysis, a bodily process that naturally breaks up clots. The smooth muscle in blood vessel walls was relaxed by a plant extract; it stopped blood vessels from narrowing and restricting blood flow to all body organs. According to separate findings by Zhang *et al.*, the growth of aortic smooth muscle cells is inhibited by andrographolide *in vitro*. Andrographolide may be used in patients with a variety of cardiac diseases. The aqueous fractions of water: n-butanol extract significantly lowers MAP without significantly lowering heart rate, whereas the ethyl acetate fraction and andrographolide have no effect on mean arterial blood pressure (MAP). According to reports, it boosted the uptake of labeled glucose in cultured myoblast cells, which may have an effect on lowering blood glucose levels. Researchers discovered a hypotensive effect of its aqueous extract in rats during a clinical trial, and they postulated that the aqueous extract of *Andrographis paniculata* may lower spontaneously hypertensive rats' systolic blood pressure by reducing plasma levels of angiotensin-converting enzyme and free radicals as well [80, 81].

Immunomodulatory activity

According to reports, andrographolide has immunostimulant and suppressive properties. A diterpene lactone called andrographolide has been found to have immunomodulatory properties that are linked to increased human peripheral blood lymphocyte proliferation, key cytokine production, and the total blood cells have increased immunological activation marker expression (like INF-, neopterin, and 2-microglobulin). HPBLs (human peripheral blood lymphocytes) were activated by the immune stimulatory action of andrographolide described *in vitro* PHA through increased cell proliferation and IL-2 production. Additionally, it has been noted that andrographolide prevented macrophages activated by lipopolysaccharide from producing TNF and IL-12. According to reports, the plant is a powerful immune system booster, and andrographolide can effectively suppress T-cell stimulation both *in vitro* and *vivo*, a property that may be valuable for preventing harmful T-cell reactions [82, 83].

CONCLUSION

Andrographis paniculata has traditionally been employed to treat a variety of ailments. Several numerous formulations, extracts, and pure compounds of *Andrographis paniculata* are used against various bioactivities, such as antioxidant, anti-inflammatory, anti-microbial, anti-malarial, anti-cold and fever, anti-viral, hepatoprotective, anti-fertility, anti-venom, anti-cancer, anti-diabetic, cardiovascular activity, and immunomodulatory activity. The major chemical constituents are diterpenoids, flavonoids, and polyphenols present on the aerial part of the plant. Andrographolide is one of the most prevalent and prolific diterpenoids. It treats and prevents a number of human ailments. *Andrographis paniculata* has seen a significant surge in demand in recent years due to its incredible medicinal potential. Numerous clinical trials were conducted without any negative outcomes, proving the plant's safety and significance for people. Cultivation can be an excellent alternative to satisfy business demand. To learn more about novel bioactive compounds and improve the bioactivity of the original chemicals, more research is still required.

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REFERENCES

1. Khajuria AK, Manhas RK, Kumar H, Bisht NS. Ethnobotanical study of traditionally used medicinal plants of Pauri district of Uttarakhand, India. J Ethnopharmacol. 2021 Aug 10;276:114204. doi: 10.1016/j.jep.2021.114204. PMID 34000367.
2. Shahid A. Handbook of 200 medicinal plants. Springer Science+Business Media LLC; 2020.
3. Joshi RK, Satyal P, Setzer WN. Himalayan aromatic medicinal plants: a review of their ethnopharmacology, volatile phytochemistry, and biological activities. Medicines (Basel). 2016;3(1):6. doi: 10.3390/medicines3010006, PMID 28930116.
4. Joy PP, Thomas J, Samuel M, Skaria Baby P. Impact of quebracho tannins supplementation on productive and reproductive efficiency of dairy cows. Med Plants. 1998;449-632.
5. Sharma A, Lal K, Handa SS. Standardization of the Indian crude drug kalmegh by high-pressure liquid chromatographic determination of andrographolide. Phytochem Anal. 1992;3(3):129-31. doi: 10.1002/pca.2800030308.
6. Akbar S. *Andrographis paniculata*: a review of pharmacological activities and clinical effects. Altern Med Rev. 2011;16(1):66-77. PMID 21438648.
7. Therasa Annai S, Sobiya G. Parimala Mabel S. Leaves of *Andrographis paniculata* is an antioxidant and anticancer agent. Asian J Pharm Clin Res. 2020;13(8):213-7.
8. Tomar GS, Tiwari SK, Chaturvedi GN. Kalmegh (*Andrographis paniculata* Nees) and its medicinal status. Nagarjun. 1982 Dec:76-8.
9. Saxena S, Jain DC, Bhakuni RS, Sharma RP. Chemistry and pharmacology of *Andrographis* species. Indian Drugs. 1998;35:458-67.
10. Perry LM. Medicinal plants of East and Southeast Asia: attributed properties and uses. Cambridge: MIT Press; 1980.
11. Poolsup N, Suthisisang C, Prathanturarug S, Asawamekin A, Chanchareon U. Andrographis paniculata in the symptomatic treatment of uncomplicated upper respiratory tract infection: systematic review of randomized controlled trials. J Clin Pharm Ther. 2004;29(1):37-45. doi: 10.1046/j.1365-2710.2003.00534.x, PMID 14748896.
12. Chopra RN. Glossary of Indian medicinal plants. New Delhi: Council for Scientific and Industrial Research; 1980. p. 18.
13. Cheung HY, Cheung CS, Kong CK. Determination of bioactive diterpenoids from Andrographis paniculata by micellar electrokinetic chromatography. J Chromatogr A. 2001;930(1-2):171-6. doi: 10.1016/s0021-9673(01)01160-8, PMID 11681575.
14. Chao WW, Lin BF. Isolation and identification of bioactive compounds in Andrographis paniculata (Chuanxinlian). Chin Med. 2010;5:17. doi: 10.1186/1749-8546-5-17, PMID 20465823.
15. Yang M, Wang J, Kong L. Quantitative analysis of four major diterpenoids in *Andrographis paniculata* by ^{1}H NMR and its application for quality control of commercial preparations. J Pharm Biomed Anal. 2012;70:87-93. doi: 10.1016/j.jpba.2012.05.037, PMID 22738787.
16. Wu D, Cao X, Wu S. Overlapping elution-extrusion counter-current chromatography: a novel method for efficient purification of natural cytotoxic andrographolides from Andrographis paniculata. J Chromatogr A. 2012;1223:53-63. doi: 10.1016/j.chroma.2011.12.036, PMID 22227359.
17. Aromdee C. Modifications of andrographolide to increase some biological activities: a patent review (2006–2011). Expert Opin Ther Pat. 2012;22(2):169-80. doi: 10.1517/13543776.2012.661718, PMID 22329509.

18. Zou QY, Li N, Dan C, Deng WL, Peng SL, Ding LS. A new ent-labdane diterpenoid from *Andrographis paniculata*. Chin Chem Lett. 2010;21(9):1091-3. doi: 10.1016/j.cclet.2010.05.002.
19. Shen YH, Li RT, Xiao WL, Xu G, Lin ZW, Zhao QS. Ent-labdane diterpenoids from *Andrographis paniculata*. J Nat Prod. 2006;69(3):319-22. doi: 10.1021/np050160u, PMID 16562826.
20. Ma XC, Gou ZP, Wang CY, Yao JH, Xin XL, Lin Y. A new ent-labdane diterpenoid lactone from andrographis paniculata. Chin Chem Lett. 2010;21(5):587-9. doi: 10.1016/j.cclet.2010.01.019.
21. Chen L, Zhu H, Wang R, Zhou K, Jing Y, Qiu F. Ent-labdane diterpenoid lactone stereoisomers from *Andrographis paniculata*. J Nat Prod. 2008;71(5):852-5. doi: 10.1021/np0704452, PMID 18357994.
22. Xu C, Chou GX, Wang ZT. A new diterpene from the leaves of *Andrographis paniculata* Nees. Fitoterapia. 2010;81(6):610-3. doi: 10.1016/j.fitote.2010.03.003, PMID 20230876.
23. Kuroyanagi M, Sato M, Ueno A, Nishi K. Flavonoids from *Andrographis paniculata*. Chem Pharm Bull. 1987;35(11):4429-35. doi: 10.1248/cpb.35.4429.
24. Chen LX, He H, Xia GY, Zhou KL, Qiu F. A new flavonoid from the aerial parts of *Andrographis paniculata*. Nat Prod Res. 2014;28(3):138-43. doi: 10.1080/14786419.2013.856907, PMID 24236635.
25. Bhaskar Reddy MVB, Kishore PH, Rao CV, Gunasekar D, Caux C, Bodo B. New 2′-oxygenated flavonoids from *Andrographis affinis*. J Nat Prod. 2003;66(2):295-7. doi: 10.1021/np020331k, PMID 12608871.
26. Koteswara Rao Y, Vimalamma G, Rao CV, Tzeng YM. Flavonoids and andrographolides from *Andrographis paniculata*. Phytochemistry. 2004;65(16):2317-21. doi: 10.1016/j.phytochem.2004.05.008, PMID 15381002.
27. Wu TS, Chern HJ, Damu AG, Kuo PC, Su CR, Lee EJ. Flavonoids and ent-labdane diterpenoids from Andrographis paniculata and their antiplatelet aggregatory and vasorelaxing effects. J Asian Nat Prod Res. 2008;10(1-2):17-24. doi: 10.1080/10286020701273627. PMID 18058376.
28. Gupta KK, Taneja SC, Dhar KL, Atal CK. Flavonoids of *Andrographis paniculata*. Phytochemistry. 1983;22(1):314-5. doi: 10.1016/S0031-9422(00)80122-3.
29. Kishore PH, Reddy MV, Reddy MK, Gunasekar D, Caux C, Bodo B. Flavonoids from andrographis lineata. Phytochemistry. 2003;63(4):457-61. doi: 10.1016/s0031-9422(02)00702-1, PMID 12770598.
30. Dua VK, Ojha VP, Roy R, Joshi BC, Valecha N, Devi CU. Anti-malarial activity of some xanthones isolated from the roots of Andrographis paniculata. J Ethnopharmacol. 2004;95(2-3):247-51. doi: 10.1016/j.jep.2004.07.008, PMID 15507344.
31. Xu C, Chou GX, Wang CH, Wang ZT. Rare noriridoids from the roots of *Andrographis paniculata*. Phytochemistry. 2012;77:275-9. doi: 10.1016/j.phytochem.2011.12.020, PMID 22342031.
32. Singha PK, Roy S, Dey S. Protective activity of andrographolide and arabinogalactan proteins from andrographis paniculata nees. against ethanol-induced toxicity in mice. J Ethnopharmacol. 2007;111(1):13-21. doi: 10.1016/j.jep.2006.10.026, PMID 17127022.
33. Varma A, Padh H, Shrivastava N. Andrographolide: a new plant-derived antineoplastic entity on horizon. Evid Based Complement Alternat Med. 2011;2011:815390. doi: 10.1093/ecam/nep135, PMID 19752167.
34. Zhou B, Zhang D, Wu X. Biological activities and corresponding SARs of andrographolide and its derivatives. Mini Rev Med Chem. 2013;13(2):298-309, PMID 23438057.
35. Wang T, Liu B, Zhang W, Wilson B, Hong JS. Andrographolide reduces inflammation-mediated dopaminergic neurodegeneration in mesencephalic neuron-glia cultures by inhibiting microglial activation. J Pharmacol Exp Ther. 2004;308(3):975-83. doi: 10.1124/jpet.103.059683, PMID 14718612.
36. Parichatikanond W, Suthisisang C, Dhepakson P, Herunsalee A. Study of anti-inflammatory activities of the pure compounds from andrographis paniculata (burm. f.) nees and their effects on gene expression. Int Immunopharmacol. 2010;10(11):1361-73. doi: 10.1016/j.intimp.2010.08.002, PMID 20728594.
37. Sule A, Ahmed QU, Latip J, Samah OA, Omar MN, Umar A. Antifungal activity of *Andrographis paniculata* extracts and active principles against skin pathogenic fungal strains *in vitro*. Pharm Biol. 2012;50(7):850-6. doi: 10.3109/13880209.2011.641021, PMID 22587518.
38. Chen J, Xue H, Ye W, Fang B, Liu Y, Yuan S. Activity of andrographolide and Its derivatives against influenza virus *in vivo* and *in vitro*. Biol Pharm Bull. 2009;32(8):1385-91. doi: 10.1248/bpb.32.1385.
39. Wiart C, Kumar K, Yusof MY, Hamimah H, Fauzi ZM, Sulaiman M. Antiviral properties of ent-labdene diterpenes of andrographis paniculata nees, inhibitors of herpes simplex virus type 1. Phytother Res. 2005 Dec;19(12):1069-70. doi: 10.1002/ptr.1765, PMID 16372376.
40. Madav S, Tripathi HC, Mishra SK. Analgesic, antipyretic and antiulcerogenic effects of andrographolide. Indian J Pharm Sci. 1995;57(3):121-5.
41. Lim JC, Chan TK, Ng DS, Sagineedu SR, Stanslas J, Wong WS. Andrographolide and its analogues: versatile bioactive molecules for combating inflammation and cancer. Clin Exp Pharmacol Physiol. 2012;39(3):300-10. doi: 10.1111/j.1440-1681.2011.05633.x. PMID 22017767.
42. Lee YC, Lin HH, Hsu CH, Wang CJ, Chiang TA, Chen JH. Inhibitory effects of andrographolide on migration and invasion in human non-small cell lung cancer A549 cells via down-regulation of PI3K/Akt signaling pathway. Eur J Pharmacol. 2010;632(1-3):23-32. doi: 10.1016/j.ejphar.2010.01.009, PMID 20097193.
43. Burgos RA, Loyola M, Hidalgo MA, Labranche TP, Hancke JL. Effect of 14-deoxyandrographolide on calcium-mediated rat uterine smooth muscle contractility. Phytother Res. 2003;17(9):1011-5. doi: 10.1002/ptr.1275, PMID 14595578.
44. Yu BC, Chang CK, Su CF, Cheng JT. Mediation of β-endorphin in andrographolide-induced plasma glucose-lowering action in type I diabetes-like animals. Naunyn Schmiedebergs Arch Pharmacol. 2008;377(4-5):529-40.
45. Qin LH, Kong L, Shi GJ, Wang ZT, Ge BX. Andrographolide inhibits the production of TNF-alpha and interleukin-12 in lipopolysaccharide-stimulated macrophages: role of mitogen-activated protein kinases. Biol Pharm Bull. 2006;29(2):220-4. doi: 10.1248/bpb.29.220, PMID 16462022.
46. Woo AYH, Waye MMY, Tsui SKW, Yeung STW, Cheng CHK. Andrographolide up-regulates cellular-reduced glutathione level and protects cardiomyocytes against hypoxia/reoxygenation injury. J Pharmacol Exp Ther. 2008;325(1):226-35. doi: 10.1124/jpet.107.133918, PMID 18174384.
47. Tan ML, Kuroyanagi M, Sulaiman SF, Najimudin N, Muhammad TST. Cytotoxic activities of major diterpenoid constituents of andrographis paniculata in a panel of human tumor cell lines. Pharm Biol. 2005;43(6):501-8. doi: 10.1080/13880200500220557.
48. Sheeja K, Guruvayoorappan C, Kuttan G. Antiangiogenic activity of *Andrographis paniculata* extract and andrographolide. Int Immunopharmacol. 2007;7(2):211-21. doi: 10.1016/j.intimp.2006.10.002, PMID 17178389.
49. Naik SR, Hule A. Evaluation of immunomodulatory activity of an extract of andrographolides from andographis paniculata. Planta Med. 2009;75(8):785-91. doi: 10.1055/s-0029-1185398, PMID 19263340.
50. Handa SS, Sharma A. Hepatoprotective activity of andrographolide from andrographis paniculata against carbontetrachloride. Indian J Med Res. 1990;92:276-83. PMID 2228074.
51. Chander R, Srivastava V, Tandon JS, Kapoor NK. Antihepatotoxic activity of diterpenes of *Andrographis paniculata* (Kal-Megh) against plasmodium berghei-induced hepatic damage in Mastomys natalensis. Int J Pharmacogn. 1995;33(2):135-8. doi: 10.3109/13880209509055213.
52. Verma N, Vinayak M. Antioxidant action of *Andrographis paniculata* on lymphoma. Mol Biol Rep. 2008;35(4):535-40. doi: 10.1007/s11033-007-9119-x, PMID 17805989.
53. Das S, Gautam N, Dey SK, Maiti T, Roy S. Oxidative stress in the brain of nicotine-induced toxicity: protective role of Andrographis paniculata Nees and vitamin E. Appl Physiol Nutr Metab. 2009;34(2):124-35. doi: 10.1139/H08-147, PMID 19370042.

54. Ahmad Sultan, Ahmad Sheeba, Mohammad Arshad, Afxal Ahmad MS, Ahmad S, Arshad M, Afzal M. Andrographia paniculata a miracle herb for cancer treatment: *in vivo* and *in vitro* studies against Aflatoxin B1 toxicity. Egypt J Med Hum Genet. 2014;15(2):163-71. doi: 10.1016/j.ejmhg.2013.12.006.
55. Lin FL, Wu SJ, Lee SC, Ng LT. Antioxidant, antioedema and analgesic activities of Andrographis paniculata extracts and their active constituent andrographolide. Phytother Res. 2009;23(7):958-64. doi: 10.1002/ptr.2701, PMID 19142986.
56. Chiou WF, Chen CF, Lin JJ. Mechanisms of suppression of inducible nitric oxide synthase (iNOS) expression in raw 264.7 cells by andrographolide. Br J Pharmacol. 2000;129(8):1553-60. doi: 10.1038/sj.bjp.0703191, PMID 10780958.
57. Shen YC, Chen CF, Chiou WF. Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect. Br J Pharmacol. 2002;135(2):399-406. doi: 10.1038/sj.bjp.0704493, PMID 11815375.
58. Hidalgo MA, Romero A, Figueroa J, Cortees P, Concha II, Hancke JL, Burgos RA. Andrographolide interferes with the binding of nuclear factor-κB to DNA in HL-60-derived neutrophilic cells. Br J Pharmacol. 2005;144(5):680-6. doi: 10.1038/sj.bjp.0706105, PMID 15678086.
59. Prabasheela B, Venkateshwari R, Nivetha S, Mohana PP, Jayashree T, Vimala R, Karthik K. Phytochemical analysis and antioxidant activity of arachis hypogeal. J Chem Pharm Res. 2015;7(10):116-21.
60. Liu J, Wang ZT, Ji LL. *In vivo* and *in vitro* anti-inflammatory activities of neoandrographolide. Am J Chin Med. 2007;35(2):317-28. doi: 10.1142/S0192415X07004849, PMID 17436371.
61. Chao WW, Kuo YH, Hsieh SL, Lin BF. Inhibitory effects of ethyl acetate extract of *Andrographis paniculata* on NF-κB trans-activation activity and LPS-induced acute inflammation in mice. Evid Based Complement Alternat Med. 2011;2011:254531. doi: 10.1093/ecam/nep120, PMID 19745004.
62. Singha PK, Roy S, Dey S. Antimicrobial activity of *Andrographis paniculata*. Fitoterapia. 2003;74(7-8):692-4. doi: 10.1016/s0367-326x(03)00159-x, PMID 14630176.
63. Mishra K, Dash AP, Swain BK, Dey N. Anti-malarial activities of *Andrographis paniculata* and Hedyotis corymbosa extracts and their combination with curcumin. Malar J. 2009;8:26. doi: 10.1186/1475-2875-8-26, PMID 19216765.
64. Shukla B, Visen PK, Patnaik GK, Dhawan BN. Choleretic effect of andrographolide in rats and guinea pigs. Planta Med. 1992;58(2):146-9. doi: 10.1055/s-2006-961416, PMID 1529026.
65. Choudhury BR, Poddar MK. Andrographolide and kalmegh (*Andrographis paniculata*) extract: *in vivo* and *in vitro* effect on hepatic lipid peroxidation. Methods Find Exp Clin Pharmacol. 1984;6(9):481-5. PMID 6513681.
66. Zheng ZY. Pharmacokinetic studies on 3H-andrographolide. Chinese Herbal Med. 1982;13:33-6.
67. Akbarsha MA, Murugaian P. Aspects of the male reproductive toxicity/male antifertility property of andrographolide in albino rats: effect on the testis and the cauda epididymidal spermatozoa. Phytother Res. 2000;14(6):432-5. doi: 10.1002/1099-1573(200009)14:6<432::aid-ptr622>3.0.co;2-i, PMID 10960897.
68. Zoha MS, Hussain AH, Choudhury SA. Antifertility effect of *Andrographis paniculata* in mice. Bangladesh Med Res Council Bull. 1989;15(1):34-7. PMID 2818412.
69. Najib Nik A, Rahman N, Furuta T, Najib Nik A, Rahman N, Furuta T, Kojima S, Takane K, Ali Mohd M. Antimalarial activity of extracts of Malaysian medicinal plants. J Ethnopharmacol. 1999;64(3):249-54. doi: 10.1016/s0378-8741(98)00135-4, PMID 10363840.
70. Cáceres DD, Hancke JL, Burgos RA, Wikman GK. Prevention of common colds with Andrographis paniculata dried extract. A Pilot double blind trial. Phytomedicine. 1997;4(2):101-4. doi: 10.1016/S0944-7113(97)80051-7. PMID 23195395.
71. Roxas M, Jurenka J. Colds and influenza: a review of diagnosis and conventional, botanical, and nutritional considerations. Altern Med Rev. 2007;12(1):25-48. PMID 17397266.
72. Thamlikitkul V, Dechatiwongse T, Theerapong S, Chantrakul C, Boonroj P, Punkrut W. Efficacy of *Andrographis paniculata*, nees for pharyngotonsillitis in adults. J Med Assoc Thai. 1991;74(10):437-42. PMID 1797953.
73. Calabrese C, Berman SH, Babish JG, Shinto X Ma L, Dorr M, Wells K, Wenner CA, Standish LJ, Calabrese C, Berman SH, Babish JG, Ma X, Shinto L, Dorr M. A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother Res. 2000;14(5):333-8. doi: 10.1002/1099-1573(200008)14:5<333::aid-ptr584>3.0.co;2-d, PMID 10925397.
74. Biological activities of Kalmegh (*Andrographis paniculata* Nees) and its active principle-a review. Indian J Nat Prod Resour. 2010;1(2):125-35.
75. Chang RS, Ding L, Chen GQ, Pan QC, Zhao QCZL, Smith KM. Dehydroandrographolide succinic acid monoester as an inhibitor against the human immunodeficiency virus. Proc Soc Exp Biol Med. 1991;197(1):59-66. doi: 10.3181/00379727-197-43225, PMID 1708503.
76. Premendran JSSJ, Salwe JKKJ, Pathak S, Brahmane R, Manikmekalai K. Anti-cobra venom activity of plant *Andrographis paniculata* and its comparison with polyvalent anti-snake venom. J Nat Sci Biol Med. 2011;2(2):198-204. doi: 10.4103/0976-9668.92326, PMID 22346236.
77. Brahmane RI, Pathak SS, Wanmali VV, Salwe KJ, Premendran SJ, Shinde BB. Partial *in vitro* and *in vivo* red scorpion venom neutralization activity of Andrographis paniculata. Pharmacognosy Res. 2011;3(1):44-8. doi: 10.4103/0974-8490.79115. PMID 21731395.
78. Singh RP, Banerjee S, Rao AR. Modulatory influence of andrographis paniculata on mouse hepatic and extrahepatic carcinogen metabolizing enzymes and antioxidant status. Phytother Res. 2001;15(5):382-90. doi: 10.1002/ptr.730, PMID 11507728.
79. Reyes BA, Bautista ND, Tanquilut NC, Anunciado RV, Leung AB, Sanchez GC. Anti-diabetic potentials of momordica charantia and andrographis paniculata and their effects on estrous cyclicity of alloxan-induced diabetic rats. J Ethnopharmacol. 2006;105(1-2):196-200. doi: 10.1016/j.jep.2005.10.018. PMID 16298503.
80. Liu J, Wang ZT, Ge BX. AndrograpaninGe BX, isolated from *Andrographis paniculata*, exhibits anti-inflammatory properties in lipopolysaccharide-induced macrophage cells through down-regulating the p38 MAPKs signaling pathways. Andrograpanin, isolated from Andrographis paniculata, exhibits anti-inflammatory property in lipopolysaccharide-induced macrophage cells through down-regulating the p38 MAPKs signaling pathways. Int Immunopharmacol. 2008;8(7):951-8. doi: 10.1016/j.intimp.2007.12.014, PMID 18486905.
81. Zhang CY, Tan BK. Mechanisms of cardiovascular activity of Andrographis paniculata in the anaesthetized rat. J Ethnopharmacol. 1997;56(2):97-101. doi: 10.1016/s0378-8741(97)01509-2, PMID 9174969.
82. Ma X, Rininger J, Chigurupati P, Dong H, Babish JG. Biochemical pathways of inhibiting human immunodeficiency virus-1 replication and cytopathic by andrographolide. In: Gen Meet Am Soc Microbiol. 1997;97:538.
83. Chandrasekaran CV, Gupta A, Agarwal A. Effect of an extract of *Andrographis paniculata* leaves on inflammatory and allergic mediators *in vitro*. J Ethnopharmacol. 2010;129(2):203-7. doi: 10.1016/j.jep.2010.03.007, PMID 20307638.
84. Jayakumar T, Hsieh CY, Lee JJ, Sheu RJ. Experimental and clinical pharmacology of *Andrographis paniculata* and its major bioactive phyto constituent aandrographolide. Evid Based Complement Alternat Med. 2013;203:846740.
85. Najila MJS, Noor RA, Mohamad KAG, Syed ZSI, Khozirah S, Lokman HS, Zakiah I, Azizol AK, Siti Najila MJ, Noor Rain A, Mohamad Kamel AG, Syed Zahir SI, Khozirah S, Lokman Hakim S. The screening of extracts from Goniothalamus scortechinii, Aralidium pinnatifidum and *Andrographis paniculata* for anti-malarial activity using the lactate dehydrogenase assay. J Ethnopharmacol. 2002;82(2-3):239-42. doi: 10.1016/s0378-8741(02)00183-6, PMID 12242001.
86. Putra AMJC, Hanafi M, Pan Y, Yanuar A. Andrographolide and its derivative–a story of antimalarial drug design and

synthesis. Int J App Pharm 2017;9(1):55-61. doi: 10.22159/ijap.2017.v9s1.55_61.

87. Rajeswari S, Vidya R, Amudha P. GCMS analysis on *Andrographis paniculata* seed extract and its anticancer activity. Int J App Pharm Thematic Spec Issue. 2022:84-8.
88. Zhang XF, Tan BK. Antihyperglycaemic and anti-oxidant properties of Andrographis paniculata in normal and diabetic rats. Clin Exp Pharmacol Physiol. 2000;27(5-6):358-63. doi: 10.1046/j.1440-1681.2000.03253.x, PMID 10831236.