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Harnessing the Therapeutical Value of Andrographis Paniculata

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ABSTRACT:

The plant Andrographis paniculata, sometimes referred to as the "King of Bitters," has long been valued for its wide range of pharmacological qualities in conventional medical systems. This review sheds insight on the various pharmacological activities of Andrographis paniculata through a scientific exploration. The bioactive components of the herb, including diterpenoids, neoandrographolide, and andrographolide, have strong immunomodulatory effects by boosting the generation of cytokines and immune cells. Additionally, the plant extract exhibits strong anti-inflammatory qualities by blocking pro-inflammatory mediators including NF-κB and COX-2, potentially providing therapeutic alternatives for inflammatory ailments. This review article shades the mechanism involved in various pharmacological activities of the plant with special reference to its toxicity concern. Special attention was given to the clinical investigation being conducted for their pharmacological applications.

INTRODUCTION

Andrographis paniculata (AP) a herbaceous plant that belongs to the family *Acanthaceae*. The lant is frequently referred to as the “king of bitters”. The plant is native of Asian tropical and subtropical regions such as India, Thailand, China and Srianka. This is also referred to as "Kalmegh" in India, and various other names in different country [1]. This plant has been explored for several pharmacological properties such as immunostimulatory [2], antiviral [3], and antibacterial [4] actions. The primary effective ingredient of this plant andrographolide has shown a wide spectrum of biological actions [5]. Researchers advise structurally altering andrographolide to produce a variety of leads because of the remarkable diversity of these biological actions. Several andrographolide derivatives have been developed recently, and their pharmacological activities have also been examined.

Andrographolide, a significant bioactive phytoconstituent of AP, is present in variety of parts of plants, however, leaves are rich of content. The chemical name of andrographolide is 3α, 14, 15, 18-tetrahydroxy-5β, 9βH, 10α-labda-8, 12-dien-16-oic acid γ-lactone, and its molecular formula and weight are $C_{20}H_{30}O_5$ and 350.4 respectively. Several other derivatives of andrographolide are demonstrated in Figure 2 [6–10]. It is freely soluble in various organic solvents, despite not being extremely soluble in water. [11]. Procedures for separating andrographolide from the leaf of AP have been described by Rajani *et al*., [8]. They used dichloromethane and methanol in 1:1 ratio to extract of andrographolide. The purity of andrographolide has been assessed using various techniques such as TLC, UV Spectrophotometry, HPLC, LCMS, and DSC [9]. This review article summarizes the various pharmacological values of AP

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extract (andrographolide) with special emphasis to the biological mechanism behind these pharmacological values. Also the article shade on the clinical interventions of the plant extract.

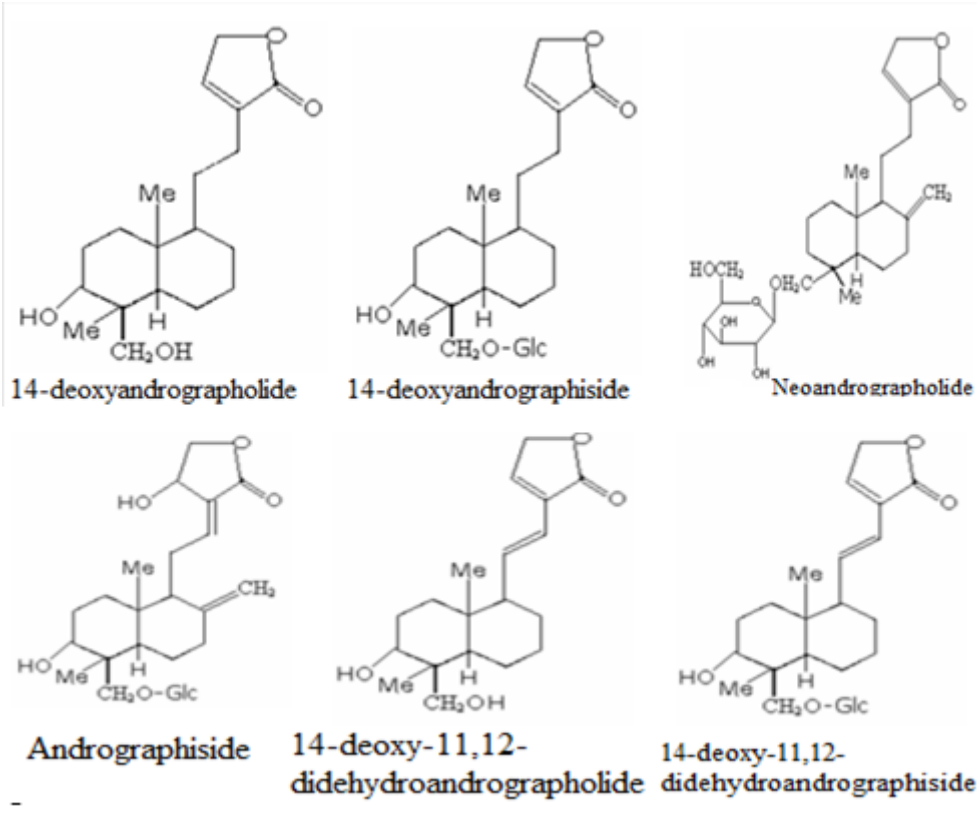

Figure 1: various derivative structure of andrographolide

PHARMACOLOGICAL ACTIVITIES

The various part of the plant has been utilized as a traditional medicine to cure several illnesses. AP has been used in pyrexia, stomachaches, inflammation, and sporadic fevers by traditional medicinal practitioners [6–9]. The entire plant has been used for several things, such as the treatment of hazardous insects, snake stings, dyspepsia, influenza, diarrhea, and respiratory tract infections [6, 7]. The extract of AP has been used as a traditional treatment for infections, illnesses that cause fevers, colic discomfort, and loss of appetite, irregular stools, and diarrhea [10, 11]. The various medical applications of AP plant parts are listed in (**Table 1**).

Table 1 Medicinal uses of A. paniculata

Parts of plant	Uses	Reference
Leaf	Fever, colic discomfort, appetite, irregular feces, diarrhea, TB and other disorders.	[12,13]
Aerial part	Urinary tract infections, malaria, high blood pressure, diabetes, and cancer.	[13]
Root	Anthelmintics.	[6]

Plant AP has been explored for several pharmacological effects and has traditional value. Here few pharmacological activities of the plant are discussing:

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1. Effect of antioxidant: Antioxidant defense mechanisms might only stop oxidative damage by preventing the reactive oxygen species [14]. The antioxidant effects of the plant have been proven in numerous investigations [15]. Aqueous extract of the plant was found to lower the level of glutathione and significantly improve the level of catalase, superoxide dismutase, and glutathione-transferase behavior showing its antioxidant properties [16]. The extract effectively reduces lipid peroxidation (in comparison to normal rats) by reducing the concentrations of thiobarbituric acid-reactive compounds in diabetic rats. Hepatic glutathione concentration was also increased [2]. Andrographolide treatment was effectively reducing the amount of phorbol-12-myristate-13-acetate (PMA)-induced reactive oxygen species and N-formyl-methionyl-leucyl-leucyl-phenylalanine (fMLP)-induced neutrophil bond in rats [17]. The prospective medicine andrographolide produces free radicals, which lowers the degree of oxidative stress and reduces the formation of compounds that are thiobarbituric acid reactive [18].

2. Anti-Inflammatory Effects: According to studies, andrographolide considerably decreases the inflammation brought by histamine, dimethylbenzene, and adrenaline [19]. The isomerism forms of enzyme nitric oxide synthase and cyclooxygenase-2 is the main key factors in more production of nitric oxide and prostaglandin E2, which is a key component of activated macrophages inflammatory activities. Lipopolysaccharide induces iNOS, which leads to an increase in NO production, by stimulating and promoting the secretion of proinflammatory cytokines from macrophages. It has been observed that LPS-stimulated NO generation is inhibited by andrographolide [20, 21]. According to Chiou *et al.*, [22], andrographolide inhibits lipopolysaccharide-induced nitric oxide synthesis production in murine macrophage like cell line RAW 264.7. Maximum contraction was observed in the part thoracic aorta to phenylephrine after being incubated with LPS was completely recovered in rats after receiving andrographolide, and the rats' decreased mean arterial blood pressure was also reduced. Additionally, andrographolide has been implicated in blocking T-cell proliferation and IL-2 generation in mixed lymphocyte reactions, as well as dendritic cell maturation and antigen presentation [23].

3. Anticancer activity: The various naturally occurring products are used as a source of drugs for the treatment of several human ailments including cancer [15]. The many natural examples of anticancer drugs are vincristine, irinotecan, etoposide, and paclitaxel [24]. Although many medications of natural origin have been found, research for new anticancer molecules is still very important for the development of less harmful and more effective as well as to improve their variety and availability drug. When choosing plants to treat cancer, samples with pharmacological applications should be taken into consideration because many illnesses replicate disease states relevant to cancer [25]. Moreover, the plant exhibits a stronger cytotoxic effect against P388 (lymphocytic leukemia) and epidermoid leukemia cells [26]. One of the diterpenoid lactones that were obtained from the AP ethyl acetate fraction showed anticancer activity [27]. Additionally, by preventing cell cycle progression, this substance exhibits powerful action against colorectal carcinoma cells [28]. Andrographolide has been shown acute promyelocytic leukemic cell growth-inhibitory effect and this effect is mediated by causing cell differentiation and death [29]. Additionally, it has been demonstrated that andrographolide reduces the expression of E-selectin, which raises the possibility that it can be used as a cancer treatment against gastric cells [30]. According to animal experimental data, andrographolide inhibits the interaction between tumor-endothelial cells and endothelial cell motility [31].

4. Immunomodulatory activity: Andrographolide has been shown immuno-stimulatory effect *in-vitro* on PHA-stimulated human peripheral blood cells through increased IL-2 production and lymphocyte proliferation. Treatment with andrographolide markedly reduced *in vivo* immune responses in mice, including delayed-type hypersensitivity and antibody reactivity to a thymus-dependent antigen [32]. According to Iruretagoyena *et al.*, [33] andrographolide was found to block NF-kB by the commencement of murine DCs, additionally, proved that andrographolide has been shown more potent action against the *in-vitro* generation of IFN- and IL-2 [33]. Furthermore, andrographolide has been demonstrated to suppress lipopolysaccharide-induced macrophage TNF- and IL-12 production [34].

5. Hepatoprotective activity: AP has been used for many years in Indian medical systems as a

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hepatostimulant and hepatoprotective drug [13]. Moreover, it is a component of various polyherbal hepatoprotective formulations one of which is effective in the treatment of hepatitis B disease [35, 37]. According to this study, andrographolide was found to reduce liver problems induced by concanavalin-A [38]. According to Shukla *et al.,* [39], andrographolide has shown choleretic stimulation effects on rats. It was observed that andrographolide had a more powerful impact in comparison of standard drug silymarin against paracetamol-induced hepatotoxicity. Similarly to silymarin, andrographolide was more potent in the treatment of ethanol-induced hepatotoxicity [39]. A single dose of extract is more effective and andrographolide has been investigated in the context of hepatic microsomal lipid peroxidation caused by carbon tetrachloride (CCl4) [40].

6. Antimicrobial effects: It has been shown that AP and andrographolide showed strong antibacterial action against a wide range of microorganisms.

The andrographolide extract concentration 25 mg/mL has been shown *in-vitro* antibacterial activity against gram-positive/negative [4]. Ethanolic extract is more useful against enterohemorrhagic strains of E. coli and upper respiratory tract infections [41]. Andrographolide has been shown virucidal usefulness against type-I Herpes Simplex Virus while exhibiting no cytotoxicity [42].

7. Antiviral effects: Medicinal plant extracts have been shown antiviral effects against many types of DNA and RNA viruses. AP has shown anti-HIV (Human Immunodeficiency Virus) neutralizing properties [43]. The antiviral effect of active constituent andrographolide was studied against herpes simplex virus around the mouth or on the genitals [42], HIV [3], flaviviruses (It is a vector–borne of RNA Viruses) and pestiviruses (It is the causative agent of Hairy shaker) [44]. According to a current study, andrographolide showed significant effective results in comparision to the six others medicinal plants in terms of antiviral inhibitory activities [45].

8. Antipyretic and Analgesic effects: After 3 hours of administering brewer's yeast-induced fever to rats, it had been shown that andrographolide, at oral doses of 100 and 300mg/kg, exhibited a strong antipyretic effect [46]. Additionally, it was found the 180 or 360 mg/kg accurate doses of andrographolide is sufficient for reducing fever after the third day of administration. Additionally, according to the study conducted by Madav S. *et al.*, [47] andrographolide possess analgesic effect at a dose of 4 mg/kg in contrast to the oral dose of 300 mg/kg used in the earlier study. This difference may be caused by the various administration methods used in these studies [46].

9. Antimalarial effects: Rahman *et al.,* [48] performed the *in-vitro* and *in-vivo* studies and find out significant antimalarial effects of AP extract. It was found that's chloroform extract of AP, completely inhibited parasite multiplication at low concentration (0.05 mg/mL) within 24 h incubation period, but the same plant species' methanol extract did so at 2.5 mg/mL but under a 48 h incubation period. The higher antimalarial impact was also found during the *in-vivo* study of AP extract [49]. As well as fractions of AP that was isolated also showed antimalarial activity [50]. Misra P. *et al.,* [51] identified andrographolides, neoandrographolides, deoxyandrographolides, and andrographolides that show anti-malarial efficacy against plasmodium species.

10. Larvicidal and Ovicidal effects: In many regions of the world, traditional human communities have employed naturally occurring plant products to combat insect species and their vectors. Numerous researchers have found that the phytochemical obtained from natural sources shows deterrent effects and can operate as larvicides, insect development regulators, and repellents [51]. AP extracts significantly impacted the process of larva development of *Anopheles stephensi* and this is a dose-dependent way, led to deformity and mortality [52]. *Aedes stephensi* were subjected to a moderate amount of ovicidal activity from AP ethanolic extract, but this impact was delayed and the result was significantly improved in the larval progression. [53].

11. Antifertility Effects: Many plants have been used to create antifertility products. In ancient Indian literature, many plants are said to show infertile properties [54]. Several plants have been examined in the lab for their antifertility properties and during the investigation of AP extract, impacts were shown on both male and female reproductive systems [55]. The study has shown an antifertility effect in mice but not in female mice when administered orally [56]. Additionally, it has been observed that AP extract causes abortions when administered to pregnant rabbits and as well as inhibits the development of human

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placental cells [57]. Suspension dose of andrographis powder 2g/kg bw/day showed infertility on the tested subject. Rats receiving oral dosages of 200, 600, or 2000 mg/kg during the first 19 days of pregnancy showed no influence on the raised progesterone level in their blood plasma [58]. According to animal research at high doses (20 mg/rat), AP extract shows contraceptive or antifertility effects [59, 60]. The number and mobility of sperm were not adversely affected by treatment with andrographolide (50mg/kg) for up to 8 weeks [61]. According to a study, andrographolide may be able to treat diminished libidos disorder and minimize mental and physical sexual activity in people with low testosterone levels by restoring hormone levels to normal.

12. Antihyperglycemic Activities: The extract of AP has been used to protect non-diabetic rabbits against oral glucose-induced hyperglycemia. No impact on fasting blood glucose levels was seen after six weeks of chronic treatment of the extract [62]. However, a decrease of 49.8% in fasting blood triglyceride levels was observed after giving an ethanolic extract of AP twice daily or two weeks in diabetic rat [21]. Blood glucose levels were reduced by 52.9% in streptozotocin-diabetic rats after administration of AP extract (50 mg/kg) to the animals. The plant material dry powder dramatically reduced blood sugar level to 61.8% when given a lesser dose of 6.25 mg/kg [63]. Dandu and Inamdar [64] reported comparable outcomes after administering an oral aqueous extract of the drug. When animals were given 400 mg/kg of streptozotocin, it was shown that increased the enzyme activity and reduced blood glucose levels in animals. Oral administration of the decoction dramatically decreased food and water intake in diabetic rats with alloxan-induced diabetes as well as decreased blood glucose levels [65]. Diabetic rats who received treatment showed a decrease from 8 to 5 days of long mean estrous cycle [64]. It showed a decrease in the plasma glucose level of a diabetic rat when given a dose-dependent treatment to a normal rat [66]. A study on rats with normoglycemia found that the water extract did not affect lowering blood sugar levels [65].

CLINICAL STUDIES

1. ***Antidiarrheal Effects.*** Diarrhea is the main cause of death in the entire world. Mainly its prey under the age of five in developed nations, and include causes such as infectious diseases, plant poisons or digestive problems [67]. Kaolin-pectin, bismuth, loperamide, and many other drugs have been used for a long time as Western medicament to treat the symptoms but have their drawbacks. Ethanolic extract of AP had 91.3% active effect in acute gastroenteritis cases and 88.3% of acute bacillary dysentery [57]. 91% of instances of acute bacillary dysentery were reported to be cured by the administration of andrographolide. The same therapeutic values were observed (91.1%) in instances of bacillary dysentery by mere use of both active moiety in a ratio (7: 3). This was stated to have higher cure rates than those attained with chloramphenicol or furazolidone [57]. This substance has also been successfully utilized in situations of overall weakness during convalescence following fever, liver problems, and advanced stages of dysentery. Traditionally it is used to sluggish life as an antidote for colic dysentery and dyspepsia. The fresh juice of A. paniculata leaves is often used in colic discomfort, appetite loss, irregular stools, and diarrhea [68].

2. ***Effects on Upper Respiratory Tract Infections.*** Many people have used AP extract to treat respiratory infections. In a clinical report, AP extract was administered to152 individuals with pharyngotonsillitis 6g/day of for 7 days [50]. In a duration-dependent manner, the effectiveness of AP extract was compared to that of acetaminophen in reducing fever [69]. They observed that a 4-day administration of AP extract treatment considerably reduced the severity of all symptoms compared to the 2-day group.

DOSAGE AND SAFETY OF ANDROGRAPHOLIDE

Administration of AP is incredibly harmless in case of toxicity even at higher dosages of 1500-2000 mg as a daily dose on rats over a period of 6 weeks. Sakila S. *et al.,* [70] even at a high drug concentration of AP extract, provided animal antifertility trial revealed no harm. Andrographolide intraperitoneal LD_{50} in male mice was estimated to be 11.46 g/kg [71]. Despite some increases in CD_4^+ count, the study was stopped early due to widespread adverse effects. When given intravenously to rabbits, andrographolide (10 mg/kg) did not cause any unusual cardiovascular reactions. Many organs were healthy according to the results of liver enzyme testing [72]. No casualties were seen on these mice when oral plant extract was given for (10

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g/kg) for 7 days daily. In a different toxicity study, conducted on rats and rabbits, andrographolide was administered orally (1g/kg) observed no any changes in animal organs [60]. According to enzymatic assays in liver and kidney organs, Singha et al., [73] found pretreatment dose, could minimize the toxicity shown in (**Table 2)**.

Our most recent research demonstrates that andrographolide significantly reduces thromboembolism by preventing thromboembolism in mice exposed to ADP (700 mg/kg) at concentrations of 22g/kg and 55g/kg, respectively. Suo *et al.*, [74] studied the pharmacokinetics (10mg/kg, i.v.), the blood concentration was found to be around 11g/mL (almost 30 µM) andrographolide. Additionally, at doses between 35 and 150 mM, andrographolide administration has no deleterious effects on platelets [75]. As a result, it is advised that andrographolide be clinically investigated as a pharmacological agent.

Table 2 Toxicity of *Andrographis paniculata* and its major natural product andrographolide

Products name	Dosage/duration/route	Experimental models	Toxic effects	References
Andrographolide	10mg/kg for 3 weeks	Human	No	3
Andrographolide	500mg/kg bw for 7 days i.p.	Mice	No	4
Andrographolide	25–75 μM	Platelets	No cytotoxicity	75
A. paniculata	20mg/kg bw for 60 days, oral	Rats	No	45
Andrographolide	22–55 μg/kg, i.v.	Mice	Lower mortality	76
A. paniculata	1 g/kg/day for 4, 6, and 8 weeks	Rats	No	74
Andrographolide	100mg/kg, i.p.	Mice	No	77
Andrographolide	10mg/kg, i.v.	Rats	No	78

i.p. = intraperitoneal, I.v. intravenous, and bw: body weight

CONCLUSION

In summary, the thorough analysis of Andrographis paniculata's pharmacological uses highlights the plant's extraordinary applicability in contemporary medicine. Andrographis paniculata presents itself as a useful pharmacological resource, with its several different activities. Its antibacterial action also strengthens its significance in preventing and treating a variety of illnesses. Andrographis paniculata presents a viable route for the development of innovative medicines across a spectrum of health disorders as research continues to uncover its medicinal potential.

LIST OF ABBREVIATIONS

AP: Andrographis paniculata, ADP: adenosine diphosphate; DMSO: dimethyl sulfoxide; i.p: intraperitoneal; i.v: intravenous; bw: body weight; LD_{50}: lethal dose.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE- Not applicable

COMPETING INTERESTS- The author has declared that no conflicts of interest exist.

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AUTHOR'S CONTRIBUTION- In the present review, MK analyzed the data related to various disease and various treatments approaches and were the most important contribution in making the manuscript. SK contributed the various dosages and safety of andrographolide approaches. NS elaborated the clinical study part in the manuscript. All authors read and approved the final manuscript.

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