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A Systematic Review on Therapeutic Potential of King of Bitters (*Andrographis paniculata -Nees*)

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ABSTRACT

Andrographis paniculata (Nees), widely known as King of bitters is the most abundantly used plant in the Indian traditional systems of medicine like Ayurveda, Siddha, and other traditional systems like Unani and Chinese medicine. *Andrographis paniculata (Nees)* is given in the form of tablets in the Indian system of medicine and the form of an injection in the Chinese system. This plant is possessing antithrombotic, immunological, anti-inflammatory, antibacterial, and hepatoprotective properties. This plant is used in folk medicines to treat diabetes and hypertension for thousands of years. The contents of diterpenoids like andrographolide, neoandrographolide and dehydroandrographolide will determine the quality of *A. paniculata*. It is a diterpene containing a γlactone ring connected to a decalin ring system via an unsaturated C-2 moiety. This plant has multiple therapeutic properties such as anti-HIV, protozoacidal, antihepatotoxic, hypotensive, anticancer, antitumor, and hypoglycemic activities. *Andrographis paniculata (Nees)* is an interesting pharmacophore with anticancer and immunomodulatory activities and hence has the potential to be developed as an anticancer chemotherapeutic agent. In this review, I have narrated the various pharmacological applications of this plant.

Abbreviations

AP, *Andrographis paniculata (Nees);* AGL, andrographoide ; NO, Nitrous oxide; PGE2, Prostaglandin E2; RA , rheumatoid arthritis; IgA, Immunoglobulin A; C4, cervical vertebra; CD4, cluster of differentiation 4; CCR5, chemokine receptor 5; CXCR4, chemokine receptor type 4; PC, prohormone proprotein convertase; IC50, The half maximal inhibitory concentration; TZM-bl cell, genetically engineered HeLa cell line; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; ACP, Acid phosphatase ; ALP, Alkaline phosphatase; HBsAg, Australia antigen; HBeAg, hepatitis B e-antigen; HBV-DNA, epatitis B virus-DNA; DNA, deoxyribonucleic acid; CCl4, Carbon tetra chloride; IL-2, interleukin 2; HPBLs, Human Peripheral Blood Lymphocyte; PKC, protein kinase C; PI3 kinase, Phosphatidylinositol-3-Kinase; Akt-MAPKs, Protein kinase B-Mitogen-activated protein kinase; MIC, minimum inhibitory concentration; HSV-1, herpes simplex virus 1; DENV1, Dengue virus 1; CPE , cytopathic effects; MNTD Maximum Nontoxic Dose ; GSH, glutathione; GSSG, Glutathione disulphide; HAEAP, hydro alcoholic extract of *Andrographis paniculata (Nees).*

1. INTRODUCTION

Andrographis paniculata (Nees) (AP) also called “King of Bitters “or Kalmegh belong to the family Acanthaceae. In Asia, it is used to treat upper respiratory tract infections and gastrointestinal ulcers, sore throat, fever, herpes, and a variety of other chronic and infectious diseases. As per Indian pharmacopeia, AP is used as a core ingredient in at least 26 Ayurvedic formulations. In Traditional Chinese Medicine (TCM), this plant is used for treating body heat and fevers, and to excrete toxins from the body. In Scandinavian countries, it is commonly used to treat common colds. [Siddhartha *et al*., 2007]

Major constituents of *A. paniculata* are diterpenoids, flavonoids, and polyphenols. The major phyto constituent of this plant is andrographolide. [Churiyah *et al*., 2015]

Figure No. 1: Aerial parts of *Andrographis paniculata (Nees)* [Churiyah *et al.*, 2015]

2. Taxonomical Classification

Kingdom: Plantae, Plants;

Subkingdom: Tracheobionta, Vascular plants;

Superdivision: Spermatophyte, Seed plants;

Division: Angiosperma

Class: Dicotyledonae

Subclass: Gamopetalae

Series: Bicarpellatae

Order: Personales

Tribe: Justicieae

Family: Acanthaceae

Genus: Andrographis

Species: paniculata

Habitat: It grows abundantly in India, Sri Lanka, Pakistan, Scandinavia, and Indonesia but it is cultivated extensively in China and Thailand, the East and West Indies, and Mauritius. [Siddhartha et al., 2007, Churiyah et al., 2015]

Synonyms: English: The Creat, King of Bitters; Hindi: Kirayat; Sanskrit: Kalmegha, Arab: Quasabhuva; Persian: Naine-havandi; Marathi: Oli-kiryata; Oriya: Tamil: Nilavembu; Bengali: Kalmegh; Gujarathi: Kariyatu; Kannada: Nelaberu; Malayalam: Kiriyattu; Bhuinimba; Bhunimba; Telugu: Nilavembu. [Churiyah et al., 2015]

3. Phytochemistry

Andrographis paniculata (Nees) contains diterpene glycosides and flavonoid glycosides. Among these, Diterpenes are the major active constituents. Flavonoids are predominantly found in roots and leaves. [Aiyalu et al., 2016]

Table No. 1: Chemical constituents

Class of chemical constituents	Name of Chemical constituents
Proteins	Albumin, Globulin, Lecithin, arabinogalactans
Bicyclic diterpenoid lactones	Andrographolide, Neoandrographolide, Dehydroandrographolide, and 14-Deoxyandrographolide
Glucosides	Deoxyandrographolide-19-beta-D-glucoside
Diterpene dimers	Bisandrographolides A, B, C and D
Flavanoids	5,7,2',3'-tetramethoxyflavanone and 5-hydroxy-7,2',3'-trimethoxyflavone

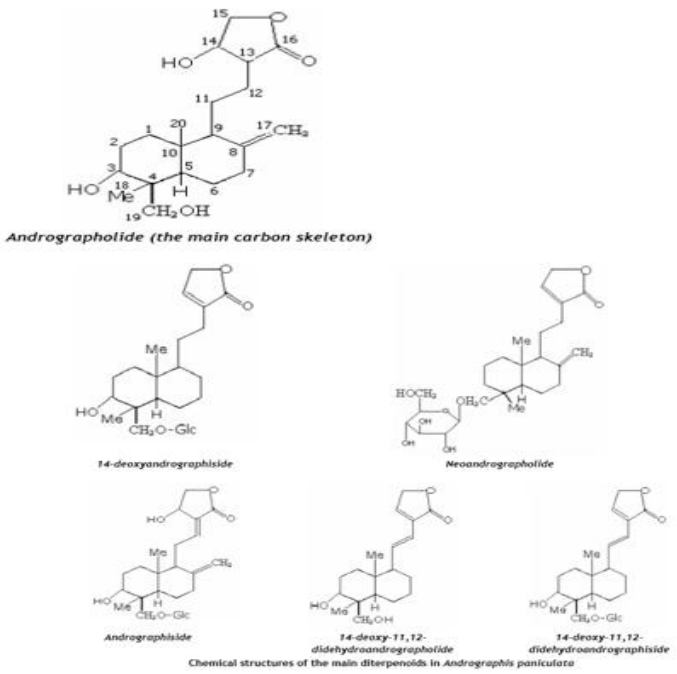

Figure No. 2: Chemical structures of the main constituents of *Andrographis paniculata (Nees)* [Aiyalu *et al*., 2016]

4. PHARMACOLOGICAL ACTIVITIES OF *ANDROGRAPHIS PANICULATA*

4.1. Anti-inflammatory activity

In a study, *Andrographis paniculata* extract and their phytoconstituents reported producing anti-inflammatory activity. The main mechanism involved with the activity is by inhibiting nitric oxide and prostaglandin production. [Gui-Fu Dai *et al*., 2011]. Anti-inflammatory effects of dimethyl benzene-induced ear edema in mice when treated with andrographolide and its derivatives were investigated and the mechanism of activity is described in a study. The mechanism involved in its anti-inflammatory activity is due to inhibition of NO and PGE2 production. [Batkhuu *et al*., 2002]. In a study, isolated diterpene lactones, neoandrographolide from the methanol extract of *Andrographis paniculata* was analyzed in a for anti-inflammatory activity. [Abu-Ghefreh *et al*., 2009] The results from the study revealed that andrographolide is responsible for the inhibition of the release of inflammatory cytokines. [Burgos *et al*., 2009]. In a prospective, randomized, double-blind, and placebo-controlled study in patients with rheumatoid arthritis (RA) Tablets (Paractin) made of an extract of *Andrographis paniculata* (30% total andrographolides) was administered three times a day for 14 weeks, after a 2-week washout period in 60 patients with active RA. Reduction of rheumatoid factor, IgA, and C4 findings was seen, suggesting that Andrographis paniculata could be a useful "natural complement" in the treatment of RA [Liu et al., 2007].

4.2. Anti-dengue activity

Anti-dengue activity in methanol extracts of *Andrographis paniculata (Nees),* on dengue virus stereotype1 (DENV-1), was carried out. From the study, it is reported that methanol extracts of Andrographis paniculata possess the ability to inhibit the activity of DENV-1 when administered as a decoction (Nilavembu Kudineer) for a scheduled period of 7 days. This study in 20 cases revealed satisfactory symptomatic relief and considerable improvement in the management of dengue fever. [Tang *et al*., 2012].

4.3. Anti-HIV activity

Immune deficiency is at the root of susceptibility to a variety of infections, and it is the basis of the Acquired Immune Deficiency Syndrome (AIDS). Impairments of immune function resulting in various clinical symptoms. HIV, like all viruses, cannot reproduce itself or even

live, without using the resources of other cells. When HIV finds a suitable cell, it attaches to the cell, using proteins on its cell surface. In the case of human cells, HIV enters the cells by binding two molecules on the cell's surface. The first of these to be identified was CD4; while the others are CCR5 and CXCR4. The brain and certain skin tissues are areas where HIV tends to focus. HIV also attacks and debilitates cells in the immune system. Helper T cells - the "T" represents the thymus gland where the cells are produced, are the main target of the virus. These cells signal the lymph nodes and the spleen to produce more antibodies against HIV. Once the antibodies inactivate the virus, suppressor T cells produce chemicals that stop further production of antibodies. HIV, however, attaches itself to the helper T cell. Through a series of manipulations of the helper cell's genetic mechanism, the virus tricks the cell into producing chemicals that the virus needs. HIV takes over the "machinery" of the helper T cell and thus becomes a virus production factory that is no longer part of the immune system. Without the T-cells, the other components of the immune system do not receive any messages to produce antibodies, and resistance to HIV is seriously compromised. Conventional treatment consists of a combination of drugs designed to achieve maximum viral suppression. Often referred to as a "cocktail," this mixture consists of compounds called protease inhibitors and reverse transcriptase inhibitors, a protease is an enzyme needed by the HIV for replication and assembly of new virus parts. Reverse transcriptase is another enzyme that HIV uses to copy its genetic material when inside the T cell. In a study, it is indicated that extracts of *Andrographis paniculata (Nees)* may have the most promising effects in the interference of the viability of HIV. Cells, when they grow and reproduce, go through a series of steps collectively termed the "cell cycle." During this process, chemical messages are carried to various parts of the cell to "turn on" functions. This process is called "signal transduction." The HIV subverts the cell's messengers, tricking them into producing more viral particles. Using signal transduction technology (methods to investigate cell message systems), researchers found that AP contained substances that destroyed the virus's communications mechanism. The main chemical moiety andrographolide from AP prevented transmission of the virus to other cells and stopped the progress of the disease by modifying cellular signal transduction. Andrographolide does this by inhibiting enzymes that facilitate the transfer of phosphates. Phosphates are molecules that are the energy storehouses of the cell. During the cell cycle, phosphates are created or chemically changed and energy is produced. This energy is used in the regulation of the cell cycle and for the many cellular functions that go on during the reproduction of the cell. AP can thus interfere with key enzymes that result in viral reproduction [Uttekar *et al*., 2012, Holt *et al*., 1998].

In a study, Neoandrographolide has shown prohormone proprotein convertase (PC) inhibitory properties with an IC50 value of 53.5 lM against furin. It is believed that this activity is exhibited by suppressing the proteolytic cleavage of envelope glycoprotein gp160 of HIV, which is known to be PC-mediated, particularly by furin and PC7. Most of the andrographolide derivatives were synthesized and examined for anti-HIV activity in TZM-bl cells. 3-Nitrobenzylidene derivative and andrographolide showed comparatively the same in vitro anti-HIV activity. [Uttekar et al., 2012].

4.4. Hepatoprotective activity

Hepatoprotective activity of *Andrographis paniculata (Nees)* is achieved by decreasing the ALT activity, decreasing liver injury, and hepatocyte apoptosis. [Maiti *et al.*, 2006] and also by decreasing GOT, GPT, ACP, ALP levels, and loss of HBsAg, HBeAg, and HBV DNA [Singha *et al*., 2007]. Effect of andrographolides on CCl4-induced oxidative stress in rats was reported [Akowuah *et al*., 2009.] Andrographolide, neoandrographolide at 6 mg/kg/day along with oral administration of kalmegh extract was administered for two weeks, the study has shown hepatoprotection against alcohol-induced and carbon tetrachloride-induced toxic effects in liver tissue. [Rana *et al.*, 1991]

4.5. Anti-microbial activity

Antimicrobial activity of leaf extract of AP was studied using different solvents like chloroform, methanol, petroleum ether, and water against bacterial strains of Bacillus subtilis and Escherichia coli by disc diffusion method. The methanolic extract was showing maximum inhibitory action against Escherichia coli and Bacillus subtilis respectively. [Neha Sinha *et al*., 2016] The most probable reason for the antibacterial activity of the methanolic extract of Kalmegh is due to the combined effect of andrographolide and arabinogalactan proteins [Lenzen, *et al*. 1998].

4.6. Anti-cancer activity

When cells develop normally, at each stage of development the cells become more specialized to be able to perform the duties of that particular cell. When carcinoma affects normal development, cells do not mature; they more closely resemble immature body cells. The more they resemble immature cells, the more vulnerable it will become for the spread of cancer. The affected cells grow and spread (metastasizes) more rapidly. If a cancer cell can

be made to mature (or differentiate), it will not have the ability to grow out of control. Researchers are desperately searching for substances that can cause cancer cells to mature. In a study in mice, to find out the naturally occurring substances that would cause differentiation of leukemia cells. Leukemia is a cancer of the white blood cells. When treated with Andrographis extract and andrographolide were known to cause differentiation of cancer cells. The results of the study demonstrated that AP had potent cell differentiation-inducing activity on leukemia cells [Matsuda et al., 1994]. AP extracts from the leaves of the plant are also cytotoxic (cell-killing) against cancer cells. This cancer cell-killing ability was demonstrated against human epidermoid carcinoma (squamous cell carcinoma) of the skin lining of the nasopharynx and lymphocytic leukemia cells. It was the andrographolide component that was found to have the cancer cell-killing ability. This ability for killing cancer cells was superior to the levels of the effectiveness recommended by the National Cancer Institute for a cytotoxic substance. [Holt et al., 1998]. A group of Japanese researchers has reported that AP stopped stomach cancer cells from multiplying. After three days of the administration, fewer than 8 cancer cells were growing in the presence of AP while the untreated cancer cells numbered 120. Laboratory tests conducted in Buffalo, New York, demonstrated that AP inhibited the growth of human breast cancer cells at levels similar to the drug tamoxifen. Extracts of AP is comparatively less toxic than most of the chemotherapeutic agents used to fight cancer. Andrographolide showed anticancer activity on diverse cancer cells representing different types of human cancers. Increasing proliferation and interleukin2 (IL-2) induction in HPBLs [Kumar et al., 2004]. Although more studies need to be done to determine just which types of cancer respond to AP, the results so far have been promising.

4.7. Antifertility Effects

AP has clear antifertility as well as pregnancy-terminating effects. In India, where AP is used for common ailments such as diarrhea, fever, and other digestive disorders, it is recommended that the herb be used only for short-term treatment. The reason being is the content of contraceptive compounds. To elucidate the actual effects on fertility, numerous studies were carried out. In one study, it was found that AP, given as dry leaf powder (105mg powder/kg body weight) each day for 60 days, stopped spermatogenesis (a process of development and maturation of sperm cells) [Akbarsha et al., 1990]. The authors revealed that antispermatogenic (sperm production blocking) or anti-androgenic (blocking effects of

androgens) ability of the plant is responsible for the anti-fertility effects in males.

Studies by Zoha and colleagues conducted in India reported antifertility effects on female mice. When 2 gm/kg body weight of sun-dried AP powder was given to the rats for six weeks, none of the animals became pregnant after mating (five times) with proven fertile males who did not receive the AP. The mice who did not receive the AP had normal litters when bred with similar males. The effect of AP in the prevention of ovulation was studied in cultured human placental tissue. The results showed that andrographolide sodium succinate (derived from AP) was effective in inhibiting human progesterone production. Progesterone is the hormone responsible for maintaining a successful pregnancy in the female.

4.8. Anti-diabetic property

In a study, the ethanol extract of *Andrographis paniculata (Nees)* in streptozotocin-induced diabetic rats was reported to decrease blood glucose level and 49.8% fasting triglyceride levels [Yu et al., 2003].

A dose-dependent antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats was observed in a study suggested that andrographolide can increase the glucose utilization to lower plasma glucose levels in diabetic rats lacking insulin [Yu et al., 2003].

4.9. Immunomodulatory activity

Andrographis paniculata (Nees) showed immunomodulatory activity by enhancing antibody production, decreasing delayed-type hypersensitivity response, increasing proliferation of human peripheral blood lymphocytes, and also increasing key cytokines and their expression [Radhika et al., 2012]. In a study the in- vitro immunomodulatory effect for andrographolide along with Kan Jang extract was evaluated, the possible mechanism is due to the production of key cytokines and immune activation markers and inhibition of spontaneous proliferation of peripheral blood lymphocytes. [Lu et al., 2012]

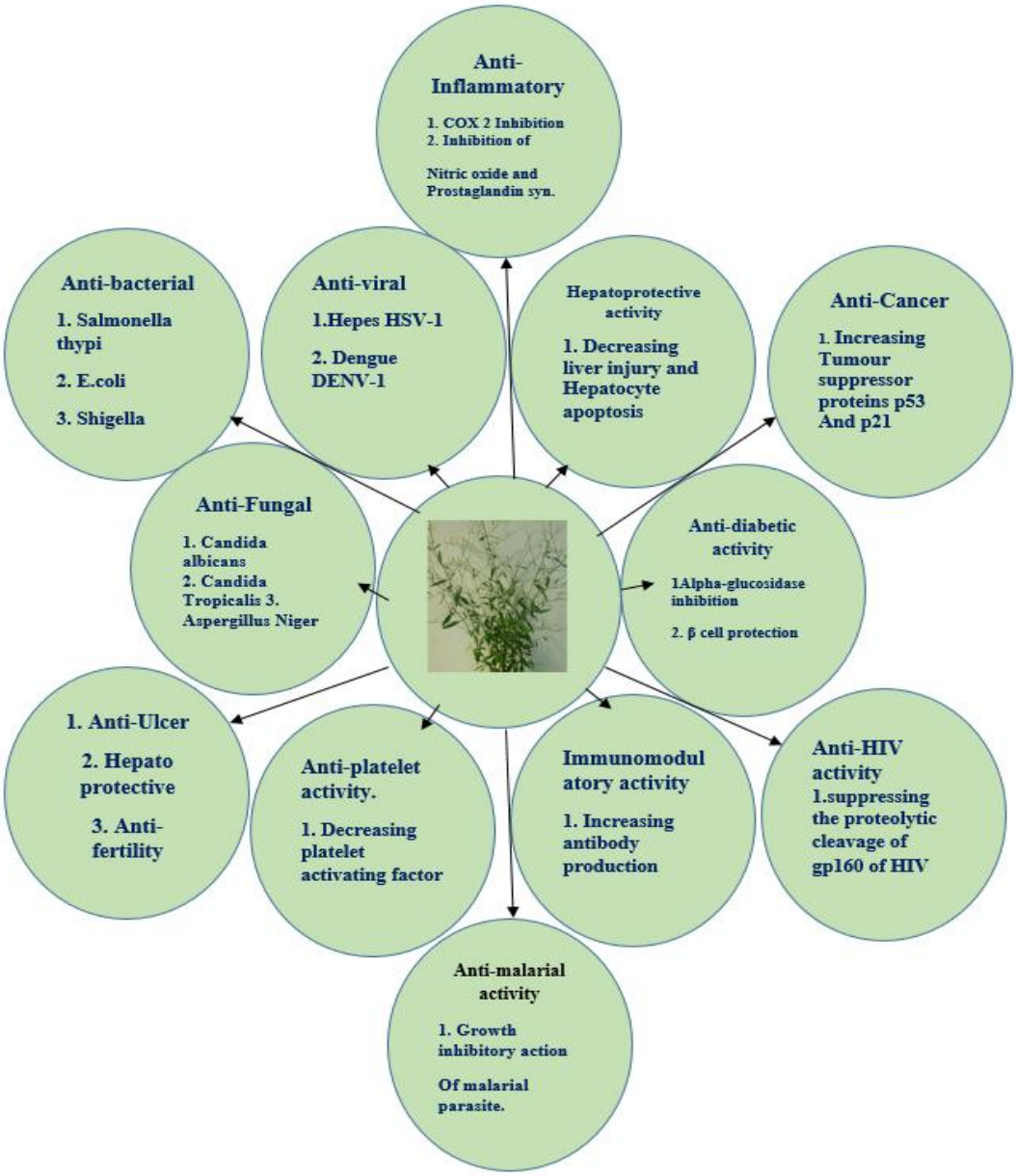

Figure No. 3: Various uses of *Andrographis paniculata (Nees)*.

5. ANTI-PLATELET ACTIVITY

The total extract and phytoconstituents of *Andrographis paniculata (Nees)* were reported to show anti-platelet activity by the various mechanism of actions. Among which decreasing platelet-activating factor and increasing eNOS-NO/cyclic-GMP pathway and by decreasing PLC2-PKC and PI3 kinase/Akt-MAPKs is predominant [Thisoda et al., 2006]. Inhibitory effect of Andrographis paniculata extract and its active diterpenoids on platelet aggregation was studied, the results indicated that andrographolide and 14-deoxy-11, and 12-didehydroandrographolide significantly inhibited thrombin-induced platelet aggregation in a

concentration and time-dependent manner while neoandrographolide had little or no activity.

5.1. Anti-malarial activity

In a study of *Andrographis paniculata (Nees)* along with Aralidium pinnatifidum and Goniothalamus scortechinii was evaluated by lactate dehydrogenase assay in Plasmodium falciparum [Najila et al., 2002] In this study, all the extracts were showing the growth inhibitory activity against malarial parasite.

5.2. Antifungal activity

Anti-fungal activity for dichloromethane and methanol extracts of *Andrographis paniculata (Nees)* by broth microdilution method against seven pathogenic fungal species were studied. In which Dichloromethane extract of A. paniculata showed the lowest minimum inhibitory concentration (MIC) (100 µg/mL) against Microsporum canis, Candida albicans, and Candida tropicalis, in contrary, methanol extract has shown lowest MIC (150 µg/mL) against C. tropicalis and Aspergillus Niger. The methanol extract of the aerial parts of the AP indicated mycelial growth obstruction of *Fusarium solani* and spore germination inhibition of Alternaria solani [Sule et al., 2003, Eugene et al., 2015].

5.3. Anti-viral activity

Andrographis paniculata (Nees) was tested for anti-viral activity against herpes simplex virus 1 (HSV-1), flaviviruses, Dengue virus (DENV1) and pestiviruses. [Chang et al., 1991]. The methanol extracts of medicinal plants viz. *Andrographis paniculata (Nees)*, Ocimum sanctum Citrus limon, Cymbopogon citratus, Momordica charantia, and Pelargonium citrosum on dengue virus serotype 1 (DENV-1). An anti-viral assay based on cytopathic effects (CPE) expressed by the degree of inhibition upon treating DENV1infected Vero E6 cells with MNTD of all six medicinal plants was showing beneficial effects against the virus. [Chellampillai et al., 2013]

5.4. Antiulcer activity

Andrographis paniculata (Nees) was evaluated by cysteamine induced duodenal ulcer model in rats. Male albino Wistar rats were pre-administered with 200 mg/kg body wt. of hydroalcoholic extract of *Andrographis paniculata (Nees)* (HAEAP) orally, for 30 days before i.p. administration of 420 mg/kg body wt. of cysteamine as a single dose. Rats pre

administered with 30 mg/kg body wt. of ranitidine served as an internal standard. Ulcer index, thiobarbituric acid reactive substances, mucin, glutathione peroxidase and myeloperoxidase activities, reduced glutathione/oxidized glutathione (GSH/GSSG) ratio, glycoproteins, and membrane-bound enzyme activities were measured in the duodenum of experimental animals. The ulcer score and myeloperoxidase activity were significantly minimized in rats treated with HAEAP. Mucin content was found to be preserved in rats treated with the extract. [Saranya et al., 2011]. In a study, the anti-ulcer effect of *Andrographis paniculata (Nees)* and andrographoide (AGL), were analyzed in albino Wistar rats. Rats pre-treated with hydroalcoholic extract of *Andrographis paniculata (Nees)* (HAEAP) (100, 200, and 500 mg/kg b.wt) or AGL (1, 3 and 5 mg/kg b. wt) orally for 30 days were subjected to pylorus ligation (PL). It reveals that HAEAP (200 mg/kg b.wt) or AGL (3 mg/kg b.wt) markedly decreased the incidence of ulcers. The test drugs were found to reduce the activities of pepsin, H+K+ATPase, and myeloperoxidase when compared to PL rats without any drug treatment. HAEAP or AGL was found to maintain the level of GSH, micin, and enzymatic antioxidants. The results indicate that the gastroprotective activity of AP and AGL may probably due to its antisecretory and antioxidant properties. [Arumugam et al., 2012]

6. ACUTE AND SUB-ACUTE TOXICITY STUDIES OF ANDROGRAPHOLIDE

When tested for acute and sub-acute toxicity tests no deaths or harmful hazardous signs were reported with *Andrographis paniculata (Nees)* and andrographolide. The test was performed in both male and female mice at a dose of 5g/kg of bodyweight. [chang et al., 1986].

7. ADVERSE EFFECTS

Andrographis paniculata (Nees) extract caused vomiting, gastric discomfort, and loss of appetite with overdosing. The most possible reason is due to the extremely bitter taste of the herb [35]. Though this plant or its extract is safe, it is not advisable to take this plant during pregnancy as it is classified under class 2b in the botanical safety handbook [McGuffin et al., 1997].

8. SUMMARY

Andrographis paniculata (Nees) is one of the most significant medicinal plants with miraculous healing powers. This plant is widely used in traditional system of medicine all

over the world. The most promising pharmacological activities such as anti-cancer, anti-HIV, Hepatoprotective, Immunomodulatory, and anti-inflammatory properties of this plant gives more scope to do systematic detail research on this medicinal herb. This review discusses a systematic approach to the medicinal chemistry, taxonomy, and therapeutic benefits of this pharmacophore.

Conflict of interest

The authors have declared that there is no conflict of interest.

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