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REVIEW ON ANDROGRAPHIS PANICULATA (Burm. f.) Nees FOR POTENTIAL IMMUNOMODULATOR ACTIVITY IN COVID -19

Jitendra Shivankar*, Chakresh Patle, Rajesh Mujariya

Institute of Pharmaceutical Science and research (IPSR), Balaghat (M.P.) India.

***Corresponding Author: Jitendra Shivankar**
Institute of Pharmaceutical Science and research (IPSR), Balaghat (M.P.) India.

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ABSTRACT
The aimed of current review to COVID-19 pandemic has intensively disrupted global health, economics, and well-being. *Andrographis paniculata* (Burm. f.) Nees has been used as a complementary treatment for COVID-19 in several Asian countries. This review aimed to summarize the information available regarding *A. paniculata* and its constituents, to provide critical points relating to its pharmacological properties, safety, and efficacy, revealing its potential to serve as a source of lead compounds for COVID-19. *A. paniculata* and its active compounds possess favorable antiviral, anti-inflammatory, immunomodulatory, and antipyretic activities that could be beneficial for COVID-19 treatment. *A. Paniculata* specially target the white blood cell and inhibit the production of T-Cell result in improvement of Immune system. *A. paniculata* alone or in combination was superior to the placebo in reducing the severity of upper respiratory tract infection. the safety of *A. paniculata*, as discussed in this review, support the argument that *A. paniculata* is a promising natural source for drug discovery regarding COVID-19 post-infectious treatment, rather than prophylaxis.

INTRODUCTION

IMMUNITY

The term immunity defines body's natural defense system against a vast array of diseases and disorders. Remarkably sophisticated and advanced among vertebrates, the complex immune system is capable to generate a limitless variety of cells and molecules to arrest enormous spectrum of infections and undesirable substances. Immunomodulators refer to those substances capable of inducing, amplifying, and inhibiting any component or phase of the immune system. Immuno stimulators and immunosuppressant are two types of immunomodulators are known for use.[5]

In fact, immune pharmacology is a newer branch of pharmacology concerned with immunomodulators. Administration of immunostimulators as in the case of AIDS and use of immunosuppressor in cases of an exaggerated response of an immune system is appreciating to reconstitute the normal immune system and increase the longevity of life. Immunomodulator intake along with antigen, the processis meant to boost the immune system, and the modulator is known as immune adjuvant. Immunology is one of the rapidly developing fields of biomedical research, holds great promises concerning various diseases and disorders. The two ways of defense of an immune mechanism involving short-term mechanism which is the first line of defense and the other highly advanced adaptive immune response marked by complexity, diversity, and memory.[5] An adaptive immune response also consists of two subtypes of immune responses, humoral immune response concerned with β-lymphocytes and cell-mediated cytotoxic response mediated by T-cells. Well, all the component cells of the immune system originate from bone marrow through hematopoiesis from bone marrow-derived stem cells. They are either developing into mature cells or migrate to other peripheral sites for migration. Besides a vast range of specialized cells of immune cells, certain molecules called cytokines which are one of the important mediators of the immune system mediate the cross talk between the specialized cells of the immune system, thereby completely integrating the behavior and action responses of the cells.[4]

Types of Immunity

There are two types of immunity: **active and passive**.

Active Immunity, results when exposure to a disease organism triggers the immune system to produce antibodies to that disease. Active immunity can be acquired through natural immunity or vaccine-induced immunity. Active immunity functions as an additional immunologic defense to eliminate infective pathogens from the body. The process is more energy-intensive compared to the innate immune response and is therefore reserved for pathogens not effectively removed by the body's initial defense

Passive Immunity. Passive immunity is provided when a person is given antibodies to a disease rather than producing them through his or her own immune system. A newborn baby acquires passive immunity from its mother through the placenta.

Immunomodulators

A substance that stimulates or suppresses the immune system and may help the body fight cancer, infection, or other diseases. Specific immunomodulating agents, such as monoclonal antibodies, cytokines, and vaccines, affect specific parts of the immune system. The drugs or agents which are use to stimulate the immunity are called as Immunomodulators agents. Immunomodulators are most often used in organ transplantation to prevent rejection of the new organ as well as in autoimmune diseases such as rheumatoid arthritis. Since the late 1960s, they have also been used to treat people with IBD, where the normal regulation of the immune system is affected. Immunomodulatory drugs modify the response of the immune system by increasing (immunostimulators) or decreasing (immune-suppressive) the production of serum antibodies.[3]

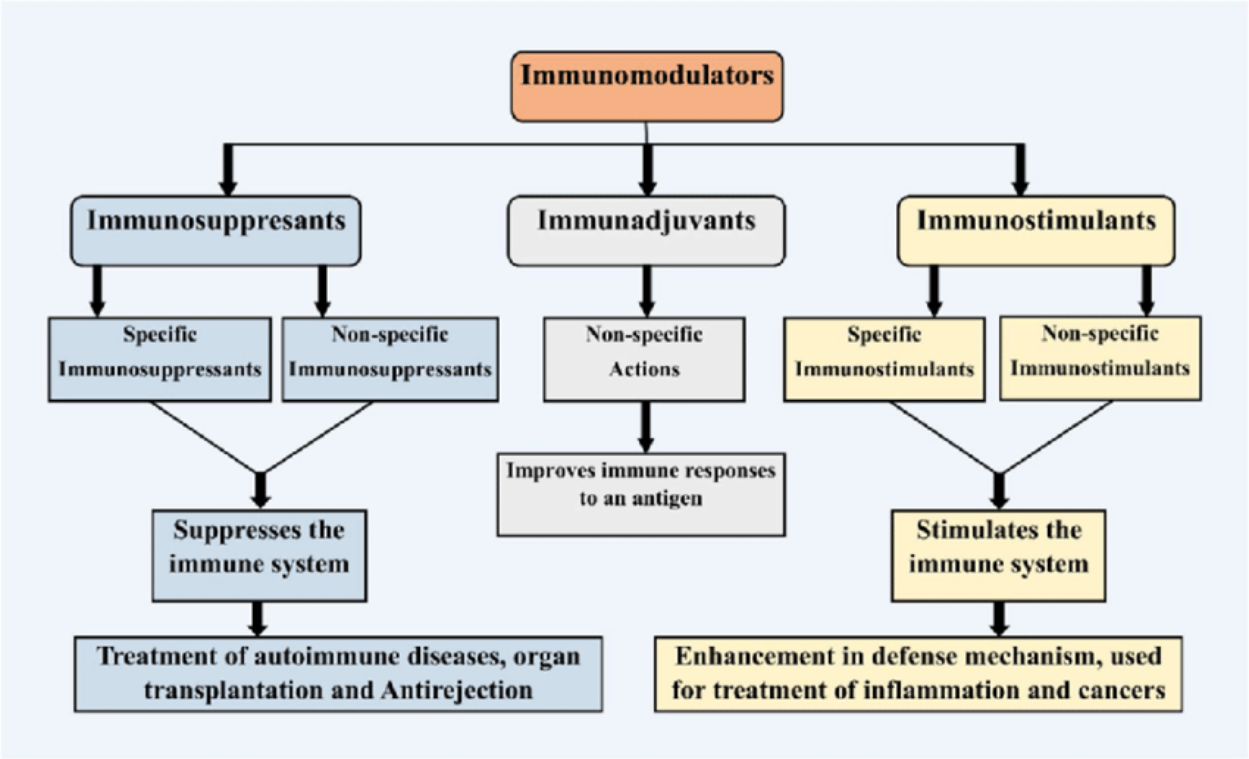


Fig. 1 - Representing classification of Immunomodulators

Mechanism of action

IMiDs enhances NK and NKT cells

The effects of IMiDs on the innate immune system, via enhancement of γδT cells, NK cells, and NKT cell function have been well documented. NKT cells are T lymphocytes which bear NK cell surface markers and recognizes glycolipid antigens (such as α-GalCer) in the context of the major histocompatibility class I-like CD1d molecules Their anti-tumour effects involve direct cytotoxic properties, IFNγ production and activation of NK cells and DC. Normally, DCs loaded with the NKT ligand α-GalCer can activate and expand NKT cells; the addition of lenalidomide not only increases the degree of DC-induced NKT cell expansion, but also NKT cell secretion of IFNγ NKT cell expansion in turn, partially accounts for the activation and proliferation of NK cells associated with IMiDs and perhaps also CD4 and CD8T cells.

NK cells have an important role in innate immunity, in killing both tumour and virus-infected cells. Thalidomide, lenalidomide and pomalidomide can increase NK cell proliferation with subsequent enhanced death of MM cell lines and primary patient cancer cells in the presence of IL-2; however, only lenalidomide and pomalidomide (but not thalidomide) have been shown to enhance antibody-dependent cellular cytotoxicity (ADCC) and natural cytotoxicity of NK cells in addition to their increase in proliferation. ADCC is a process whereby immunoglobulins attached to tumour antigens activate Fc-γ receptors on NK cells. This cross-linking triggers tumour cell cytotoxicity via perforin and granzymes released by NK cells, as well as tumour cell apoptosis induced by death ligands: FasL (Fas ligand) and TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) that are expressed on some NK cell populations. The enhanced NK cell ADCC in the presence of lenalidomide and pomalidomide corresponds

to increased NK cell FasL and granzyme B (but not perforin) expression.[6]

Through ADCC augmentation, IMiDs also enhance the cytotoxicity effects of monoclonal antibodies (of lgG1 isotype) including anti-CD40mAb (SGN-40)and anti-CD20mAb (rituximab). lenalidomide's augmentation of NK cell-specific death of rituximab-coated CD20 + cell lines was shown to be associated with increased NK cell expression of IL-8, MCP-1 and GM-CSF and decreased IL-6 expression. More recently, however, lenalidomide was shown to downregulate CD20 surface antigens in chronic lymphocytic leukaemia resulting in a net diminished rituximab-mediated ADCC. Thus, lenalidomide's net effects on ADCC are at present not fully understood and may be disease specific.[7] It is interesting to note that the *in vitro* augmentation of ADCC on NK cells by IMiDs requires both antibody (Ab) binding to Fc-γ receptors on NK cells, as well as the presence of IL-2. The presence of either IL-2R Ab, or cyclosporin-A have previously been shown to abrogate IMiDs-induced NK cell-mediated cytotoxicity, thus showing that IMIDs-induced proliferation and activation of NK cells is indeed IL-2 dependent.

Overall, *in vitro* studies so far support that IMiDs stimulate T cell and NKT cell production of IL-2 and IFNγ, resulting in potentiation of NK-cell proliferation and cytotoxicity. NK cells in turn produce T-cell- and DC-recruiting cytokines including monocyte chemotactic protein (MCP-1) and granulocyte macrophage colony-stimulating factor (GM-CSF) in response to Ab-coated target cells. This results in further chemotactic attraction of tumour-specific T cells in the presence of IMiDs.

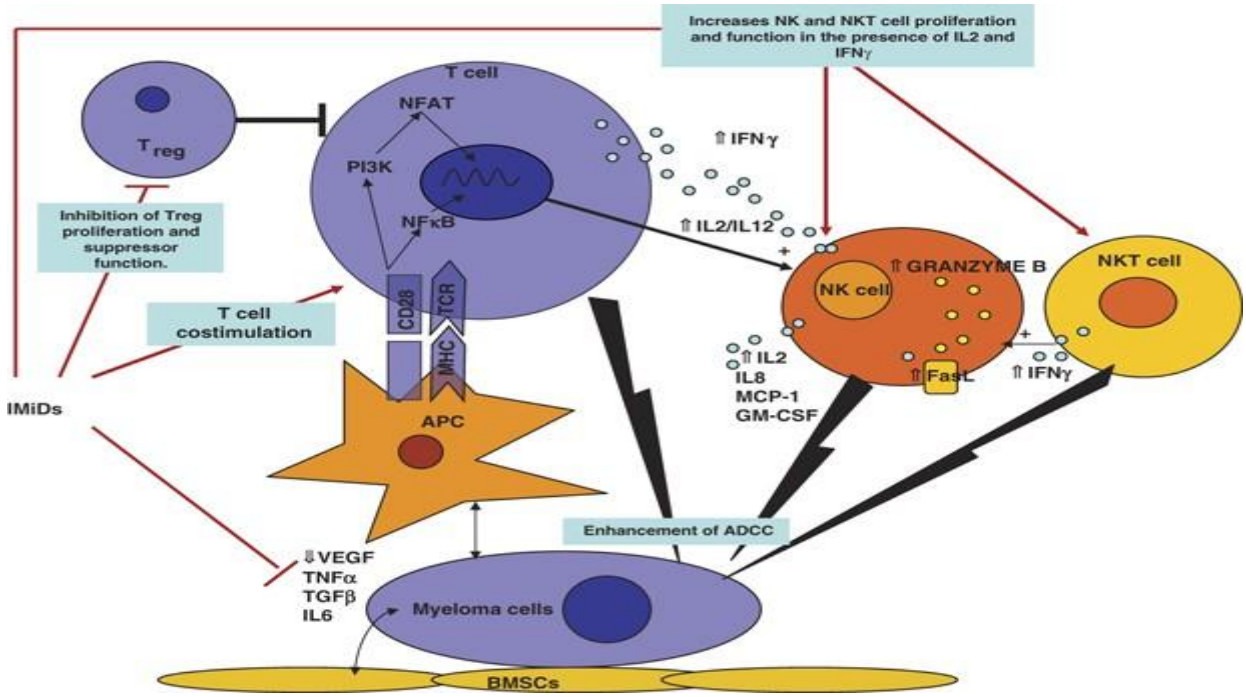


Fig. 2- Summary of the immunomodulatory effects of immunomodulatory drugs.
BMSC: bone marrow stromal cells; APC: antigen-presenting cells; IL: interleukin; TGF: transforming growth factor; TNF: tumor necrosis factor; VEGF: vascular endothelia growth factor; ADCC: antibody-dependent cellular toxicity; MHC: major histocompatibility complex; TCR: T cell receptor; NF-κB: Nuclear factor kappa B; PI3k: phosphoinositide 3-kinase; NFAT: nuclear factor of activated T cell; IFN: interferon; NK: natural killer.

Andrographis paniculate (Burm. F) Nees
Scientific classification
Kingdom :- Plantae
Division :- Magnoliophyta
Class:-Magnoliopsida
Order:-Lamiales
Family:-Acanthaceae
Genus :- *Andrographis*
Species :- *paniculata*

Andrographis paniculata (Burm. F) Nees, commonly known as the "king of bitters," is an herbaceous plant belonging to the Acanthaceae and is found throughout tropical and subtropical Asia, Southeast Asia, and India. In India, A. paniculata is known as "Kalmegh"; in China it is known as "Chuan-Xin-Lian"; in Thailand it is known as "FahTha Lai"; in Malaysia it is known as "Hempedubumi"; in Japan it is known as "Senshinren";

and in Scandinavian countries it is known as "green chiretta". Extracts of this plant and andrographolide exhibit pharmacological activities such as those that are immunostimulatory, antiviral and antibacterial. [1]As major active constituent, andrographolide exhibits a broad range of biological activities, such as anti-inflammatory, antibacterial, antitumor, antidiabetic, antimalarial, and hepatoprotective. Because of the impressive variety of these biological activities, researchers propose obtaining various leads by structurally modifying andrographolide. In recent decades, numerous andrographolide derivatives have emerged and their pharmacological activities have also been evaluated. However, studies that have comprehensively summarized or analyzed A. paniculata and its derivatives have been minimal. Therefore, to contribute to the advanced trends of research on andrographolide, this paper provides thorough information regarding the pharmacological activities of A. paniculata and its major compound andrographolide.[2]

Synonyms

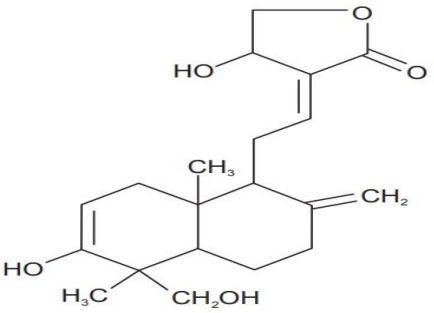
Bitterweed, King of Bitters, Creat, Green Chireta, Indian Echinachea.

Botanical Description

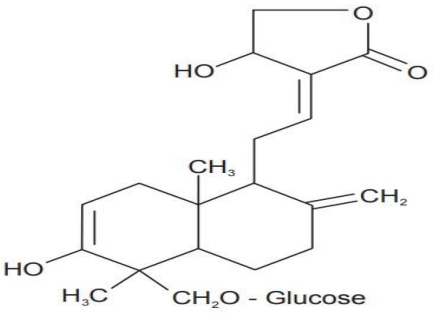
It is an erect, annual herb and 30-90 cm tall with upper part of stem quadrangular while the lower part nearly rounded stem. Leaves are opposite sessile or subsessile, linear-lanceolateorlanceolate, 3-8 cm long, acute, glabrous or minutely puberulous beneath and base cuneate, margin slightly undulate.

Distribution

Andrographis paniculata is distributed in tropical Asian countries often in isolated patches. It can be found in a variety of habitats viz. plains, hill slopes, waste lands, farms, dry or wet lands, sea shore and even road sides. Native populations of *A. paniculata* are spread throughout south India and Sri Lanka which perhaps represent the centre of origin and diversity of the species.



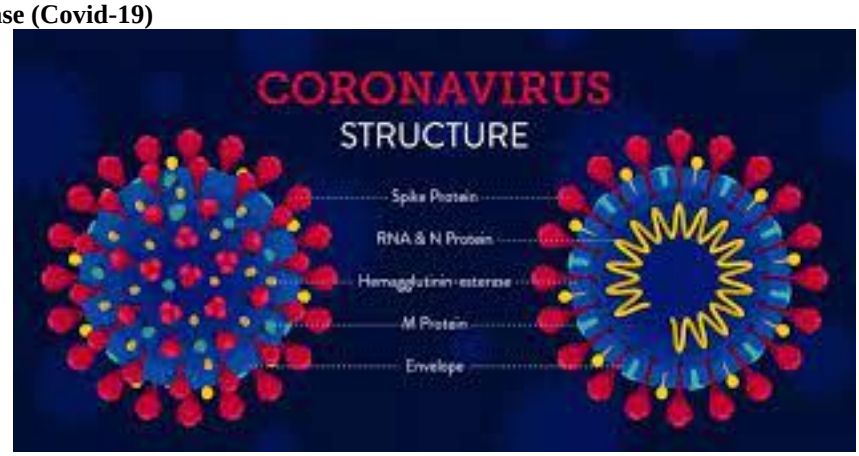
Andrographolide



Andrographiside

Morphology of the plant:- *A. paniculata* is an annual profusely branched, erect herb extremely bitter in taste. It grows to a height of 30-110 cm in moist shady places with glabrous leaves and white flowers with rose purple spots on the petal. The stem dark green, 0.4-1.0 m in height, 2-6 mm in diameter, quadrangular with longitudinal furrows and wings on the angles of the younger parts, slightly enlarged at the nodes; leaves glabrous, up to 8.0 cm long and 2.6 cm broad, lanceolate, pinnate; flowers small and solitary, corolla whitish or light pink in color with hairs, in lax spreading axillary and terminal racemes or capsules linear-oblong, acute at both ends, 1.9- 0.3 cm; seeds numerous, subquadrate, yellowish brown.[5]

Coronavirus disease (Covid-19)



Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. Most people infected with the virus will experience mild to moderate respiratory illness and recover without requiring special treatment. However, some will become seriously ill and require medical attention. Older people and those with underlying medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop serious illness. Anyone can get sick with COVID-19 and become seriously ill or die at any age.

The best way to prevent and slow down transmission is to be well informed about the disease and how the virus spreads. Protect yourself and others from infection by staying at least 1 metre apart from others, wearing a properly fitted mask, and washing your hands or using an alcohol-based rub frequently. Get vaccinated when it's your turn and follow local guidance.

The virus can spread from an infected person's mouth or nose in small liquid particles when they cough, sneeze, speak, sing or breathe. These particles range from larger respiratory droplets to smaller aerosols. It is important to practice respiratory etiquette, for example by coughing into a flexed elbow, and to stay home and self-isolate until you recover if you feel unwell.

Toxicity: Usually, a traditional dose of *A. paniculata* powder is 9–15 mg, once a day, which contains andrographolide at an amount of 90–150 mg[12]; in Chinese traditional medicine and orthodox medicine in Thailand and India, this has long been recognized as a safe amount.[13] However, when determining the safety of patients, scientists attempted to establish the toxicity data of *A. paniculata*. Toxicity studies were designed with both animals and humans. When conducted in HIV-infected patients and healthy volunteers, no toxicity was observed in an acute toxicity study of dose-escalating andrographolide, at 5 mg/kg body weight and three times a day (TID) for 3 weeks, 10 mg/kg body weight TID for a further 3 weeks, and 20 mg/kg body weight for a final 3 weeks.[14] In the animal model, Panossian et al. reported that the oral administration of A. paniculata standardized extract (andrographolide, 4.6%, and 14-deoxo-andrographolide, 2.3%) in doses of 200, 600, and 2000 mg/kg given to Wistar rats did not show toxicity [15]. Moreover, in female rats treated with standardized A. paniculata alcoholic extract (andrographolide > 30% w/w) at 5000 mg/kg, there were no treatment-necessitating toxic effects.[17] Bothiraja et al. reported that although the mice were treated with andrographolide at the maximum dose (5 g/kg), no dead mice were found.[18] Oral administration of the first true-leaf ethanolic extract of *A. paniculata* contained high levels of 14-deoxy-andrographolide but low andrographolide levels at 5000 mg/kg in mice; the results showed that all treated animals survived.[19] The median lethal dose (LD50) of *A. paniculata* extract and its andrographolide was tested in several studies, as shown in Table 2. In order to perform a subacute toxicity test, Wistar rats consumed andrographolide at 250 mg and 500 mg/kg for 21 successive days.[18] The result demonstrated that significant alterations of behavior, biochemicals, body weight gain, food intake, hematology, histopathology, mortality, and vital organ weight were undetectable.

REFERENCES

1. Identification and Quantification of Andrographolide from Andrographispaniculata (Burm. f.) Wall.exNees by RP-HPLC Method and Standardization of its Market Preparations B. K. Sajeeb, Uttom Kumar, Shimul Halder1 and Sitesh C. Bachar Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhakahttps://doi.org/10.1016/j.jopr.
2. Subramanian R, Asmawi MZ, Sadikun A. In vitro α-glucosidase and α-amylase enzyme inhibitory efects of Andrographispaniculataextract and andrographolide.ActBiochim https://doi. org/10.18388/abp.2008_3087.
3. Sheeja K, Guruvayoorappan C, Kuttan G. Antiangiogenic activity of Andrographispaniculataextract and andrographolide. Immunopharmacol. https://doi.org/10.1016/j.intimp.
4. Mishra PK, Singh RK, Gupta A, Chaturvedi A, Pandey R, Tiwari SP, Mohapatra TB. Antibacterial activity of Andrographispaniculata (Burm. f.)Wall ex Nees leaves against clinical pathogens. J Pharm Res. https://doi.org/10.1016/j.jopr.
5. Paul T, Basu S, Saha NC. Anticancer efect of Andrographispaniculata by suppression of tumor altered hypoxia signaling cascade in mouse melanoma cells. J Cancer Res Pract. https://doi.org/10.4103/ JCRP.JCRP_9_19. Low M, Khoo CS, Münch G, Govindaraghavan S, Sucher NJ. An in vitro.
6. Burgos RA, Caballero EE, Sanchez NS, Schroeder RA, Wikman GK, Hancke JL. Testicular toxicity assessment of *Andrographis paniculata* dried extract in rats. J Ethnopharmacoly.
7. T. Jayakumar, C.Y. Hsieh, J.J. Lee, J.R. Sheu, Experimental and clinical pharmacology of *Andrographis paniculata* and its major bioactive phytoconstituent *Andrographolide*, Evid base Compl Alternative Med, 2013 (2013), p. 846740.
8. M.S. Hossain, Z. Urbi, A. Sule, K.M. Hafizur Rahman, *Andrographis paniculata* (Burm. f.) Wall. exNees: a review of ethnobotany, phytochemistry, and pharmacology**,** Sci World J, 2014 (2014), p. 274905.
9. G. Davison, C. Kehaya, A. Wyn Jones, Nutritional and physical activity interventions to improve immunity, Am J Lifestyle Med, 2014; 10: 152-169.
10. Stephen H, Comac L. Miracle herbs: how herbs combine with modern medicine to treat cancer, he art disease, AIDS, and Covid more. Kensington Publishing Corporation; 2000.

11. Puri A. Immunostimulant agents from *Andrographis paniculata*. Journal of Natural Products, 1993; 56: 995–999.
12. Thamlikitkul, V.; Dechatiwongse, T.; Theerapong, S.; Chantrakul, C.; Boonroj, P.; Punkrut, W.; Ekpalakorn, W.; Boontaeng, N.; Taechaiya, S.; Petcharoen, S.; et al. Efficacy of Andrographis paniculata, Nees for pharyngotonsillitis in adults. J. Med. Assoc. Thail. = Chotmaihet Thangphaet 1991; 74: 437–442.
13. Joselin, J.; Jeeva, S. Andrographis paniculata: A Review of its Traditional Uses, Phytochemistry and Pharmacology. Med Aromatic Plants, 2014; 3: 15.
14. Calabrese, C.; Berman, S.H.; Babish, J.G.; Ma, X.; Shinto, L.; Dorr, M.; Wells, K.; Wenner, C.A.; Standish, L.J. A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother. Res., 2000; 14: 333–338.
15. Panossian, A.; Kochikian, A.; Gabrielian, E.; Muradian, R.; Stepanian, H.; Arsenian, F.; Wagner, H. Effect of Andrographis paniculate extract on progesterone in blood plasma of pregnant rats. Phytomed. Int. J. Phytother. Phytopharm., 1999; 6: 157–161.
16. Chandrasekaran, C.; Thiyagarajan, P.; Sundarajan, K.; Goudar, K.S.; Deepak, M.; Murali, B.; Allan, J.J.; Agarwal, A. Evaluation of the genotoxic potential and acute oral toxicity of standardized extract of Andrographis paniculata (KalmCold™). Food Chem. Toxicol., 2009; 47: 1892–1902.
17. Bothiraja, C.; Pawar, A.P.; Shende, V.S.; Joshi, P.P. Acute and subacute toxicity study of andrographolide bioactive in rodents: Evidence for the medicinal use as an alternative medicine. Comp. Clin. Pathol., 2013; 22: 1123–1128.
18. Worasuttayangkurn, L.; Nakareangrit, W.; Kwangjai, J.; Sritangos, P.; Pholphana, N.; Watcharasit, P.; Rangkadilok, N.; Thiantanawat, A.; Satayavivad, J. Acute oral toxicity evaluation of Andrographis paniculata-standardized first true leaf ethanolic extract. Toxicol. Rep., 2019; 6: 426–430.