INHIBITORY ACTIVITY AGAINST ALLERGIC RESPONSES AND PHARMACEUTICAL PROPERTIES OF MEMBERS OF *PHYLLANTHUS* GENUS

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Abstract

Phyllanthus (Euphorbiaceae) is widely distributed in tropical and subtropical areas, including Vietnam, where it is considered a valuable medicinal herb. Numerous bioactive compounds from Phyllanthus species have been identified, demonstrating pharmacological effects such as antiallergic, anti-inflammatory, antioxidant, antidiabetic, anticancer, antiviral, antibacterial, antimalarial, and wound healing activities. This review provides a comprehensive summary of Phyllanthus genus and its pharmaceutical properties, emphasizing the methodologies used for bioactive compound extraction and evaluation, as well as their clinical relevance.

Keywords: antiallergy, antidiabetic, antioxidant, pharmaceutical properties, *phyllanthus* genus

1. Introduction

Air pollution is a major contributing factor to the increasing prevalence of allergic diseases. Allergies impact physical and psychological health while imposing significant economic burdens (Warren *et al*., 2020). Existing treatments, including antihistamines and corticosteroids, often cause side effects such as nausea, dizziness, elevated blood pressure, and, in severe cases, myocardial infarction (Malone *et al*., 2017). This has led to a growing interest in herbal medicine, which offers safer alternatives for long-term use.

Among various natural products, *Phyllanthus* species have gained attention as potential anti-allergic agents. In Vietnam, *Phyllanthus* is traditionally used for conditions such as eczema and urticaria, while in other countries like Nepal, Malaysia, Thailand, and India, it is employed for asthma treatment (Mao *et al*., 2016). This review aims to consolidate knowledge on the biological activities of *Phyllanthus* species and explore their potential for pharmaceutical applications.

Allergy is caused by an exaggerated reaction of the immune system to harmless environmental substances, such as animal dander, house dust mites, foods, pollen, insects, and chemical agents. Specially, allergic rhinitis, asthma, and atopic eczema are among the commonest causes of chronic ill-health (Vo *et al*., 2012). Allergic diseases now affect approximately 20% of the global population, affecting the quality of life of these

individuals and their families and impacting the socio-economic welfare of society (Dierick *et al*., 2020). The diseases are increasing due to air pollution and the ambient temperature increase. Therefore, anti-allergic medicines are necessary for amelioration of allergic response of patients. Recently, natural products for prevention and/or treatment of allergic diseases have been getting much attention by researchers as well as customers due to safety and efficacy for long-term use without significant side effects. Among various natural products, *Phyllanthus* species have appeared as a potential anti-allergic herb. They have long been used as a traditional remedy for amelioration of allergic diseases, especially urticaria conditions.

2. Allergy

Allergic diseases are one of the major public health problems in the world. It was estimated that approximately one-third of the general population and one-fifth of the population in Western countries were affected by allergic diseases (Ono *et al*., 2000; Ouwehand, 2007). Specially, allergic rhinitis, asthma, and atopic eczema are among the commonest causes of chronic ill-health. The prevalence, severity, and complexity of these allergic diseases are rapidly rising and considerably adding to the burden of health-care costs (Kay, 2000). Therefore, the knowledge about the pathophysiology of allergic diseases has increased, offering new opportunities for therapeutic intervention. Substantially, allergy is caused by an exaggerated reaction of the immune system to harmless environmental substances, such as animal dander, house dust mites, foods, pollen, insects, and chemical agents (Arshad, 2010; Milián & Díaz, 2004). The initial event responsible for the development of allergic diseases is the generation of allergen-specific CD4+ Th2 cells. Once generated, effector Th2 cells produce IL-4, IL-5, IL-9, and IL-13 which cause the production of allergen-specific IgE by B cells (Akdis *et al*., 2005). Subsequently, allergic reactions are induced upon binding of allergen to IgE, which is tethered to the high affinity IgE receptor on the surface of mast cells and basophils. Following the aggregation of cell-surface receptors is a cascade of intracellular events, including the increase of intracellular Ca^{2+} level, the release of preformed inflammatory mediators from secretory granules such as histamine and β-hexosaminidase, the generation and secretion of the newly synthesized substances such as leukotrienes, prostaglandins, and cytokines. These mediators cause allergic inflammatory responses due to airway constriction, mucous production, and recruitment of inflammatory cells (Galli *et al*., 2008; Vo *et al*., 2011). According to this mechanism, the control of Th2-type cytokine expression, IgE levels, and inflammatory mediator production are especially important for the regulation of type I allergic reaction, thus allergic diseases may be managed. The current drugs that are used to treat allergies, such as antihistamines or corticosteroids, ameliorate symptoms but do not stop progression (Akdis and Akdis, 2011). There are also concerns regarding the side-effects from chronic use of current drugs, particularly by children (Li and Brown, 2009). Thus, the search for potential drug candidates containing higher anti-allergy activity is increasing in the pharmaceutical industry. In this regard, natural bioactive compounds and their derivatives are great sources for the development of new generation anti-allergic therapeutics which are more effective with fewer side-effects.

3. *Phyllanthus* species

Phyllanthus (Euphorbiaceae) consists of more than 700 species and is widely distributed in tropical and subtropical areas such as tropical Africa, tropical America, Asia, and Oceania. The plants are monoecious; leaves simple, alternate or opposite, some are leathery, flowers are very small and diclinous, they cluster in cup-shaped structures, greenish, whitish or whitish-green, often with glands. The fruit is a lobed-capsule extending from the cup and commonly the long stalk pendant. The name "*Phyllanthus"* means "leaf and flower" because the flower, as well as the fruit, seems to become one with the leaf (Awomukwu *et al*., 2015). Members of the *Phyllanthus* can be used as local medicinal practitioners ranging from headache, skin diseases to gonorrhea and syphilis. Other ailments treated with these medicinal plants include asthma, cough, diarrhea, diabetes, malaria, eye and ear problems, indigestion and constipation, nausea and vomiting, bleeding, childcare, healing of wounds and sores and tooth extraction. Some of these medicinal plants are used as styptic and as simple laxative to cure dysentery (Mao *et al*., 2016).

Phyllanthus genus present in every province in Vietnam that is considered as a precious medicinal herb for the treatment of various diseases. In Vietnam, members of *Phyllanthus* genus have been used to treat a number of diseases such as nephritis, perforated edema, kidney stones, malnourished children, enteritis, dysentery, hepatitis, boils, itchy sores, urticaria...(Do, 1997). Up to now, the chemical compositions and biological activities of some species of the *Phyllanthus* genus have been studied in Vietnam. For the first time, Ngo Van Thu and colleagues have investigated botanical characteristics of aerial parts of *Phyllanthus* spp. (25 vouchers) collected in South Vietnam (Ngo *et al*., 2009). As a result, they have identified *Phyllanthus amarus* Schum. Et Thonn, *Phyllanthus urinaria* L., and *Phyllanthus* sp. with significant differences in morphological and microscopic characters. In the study of Doan Manh Dung and colleagues, phyllanthin and hypophyllanthin have been isolated from *Phyllanthus urinaria* L. by using liquid chromatography (LC-MS/MS) with chromatography column of EC-C18 (100 × 2.1mm, 2.7µm), mobile phase of MeOH (A) – Solution (10mM ammonium acetate and 0.1% formic acid) (B) (Doan *et al*., 2018). Furthermore, Tran Thu Huyen and colleagues have developed and validated a method for quantitative analysis of phyllanthin in *Phyllanthus amarus* using ultra-performance liquid chromatography (UPLC) with fluorescence detector (Tran *et al*., 2018). The chromatographic condition was developed due to chromatography column of C18 column (1.6µm, 2.1 × 50mm), solvent system of acetonitrile:water with ratio of 55:45 (v/v), flow rate of 0.3mL/min, injection volume of 2µL, at the excitation and emission wavelengths of 230 and 340nm, respectively. In another study, nirurine, a securineage alkaloid, has been isolated from the ethanol 98% extract of the dried leaves of *Phyllanthus niruri* L. (Nguyen *et al*., 2004).

4. Phytochemical Constituents, Bioactive Compound Extraction and Evaluation Methodologies

The bioactivity of *Phyllanthus* species is largely attributed to their rich phytochemical composition, including lignans like hypophyllanthin. Hypophyllanthin has been identified as a major lignan in various *Phyllanthus* species and has been associated with several pharmacological activities. A comprehensive review discussed the immunomodulating properties of hypophyllanthin, highlighting its potential in modulating immune responses, which is crucial in managing allergic conditions (Wan Saidin *et al*., 2023).

The bioactive metabolites of these plants have high medicinal values. Scientists have been studying and reporting about the biological activity of compounds that exist in *Phyllanthus* extracts including anti-inflammatory, anticancer, antidiabetic, antidepressant, antiviral, antibacterial, antispasmodic, and antioxidant activities. More than 510 compounds with biological effects have been found and isolated from *Phyllanthus* species, most of them belong to the family of phenylpropanoids (lignins), triterpenoids, flavonoids, and tannins. The rest are sterols, alkaloids, phenols, and others. Because of various activities lignins and tannins exhibit, they are considered as representative biological active compounds of this genus. On the other hand, corilagin, geraniin and garlic acid are the compounds that receive the most attention from scientists, they are the most prevalent compounds of *Phyllanthus* genus and have been the targets of pharmacological research (Mao *et al*., 2016).

The extraction of bioactive compounds from *Phyllanthus* species involves techniques such as maceration, Soxhlet extraction, and ultrasonication, using solvents like ethanol, methanol, and aqueous solutions. Liquid Chromatography-Mass Spectrometry (LC-MS/MS) was used to isolate and quantify phyllanthin and hypophyllanthin from *Phyllanthus urinaria* (Doan *et al*., 2018). The method employed an EC-C18 chromatography column (100 × 2.1mm, 2.7µm) with a mobile phase of MeOH and 10mM ammonium acetate (0.1% formic acid). Ultra-Performance Liquid Chromatography (UPLC) was applied for phyllanthin quantification in *Phyllanthus amarus*, using a C18 column (1.6µm, 2.1 × 50mm), acetonitrile:water (55:45 v/v), and fluorescence detection (excitation/emission: 230/340nm) (Tran *et al*., 2018). Nuclear Magnetic Resonance (NMR) Spectroscopy was utilized to determine the structure of alkaloid nirurine from *Phyllanthus niruri* (Nguyen *et al*., 2004). These methodologies ensure reproducibility in bioactive compound isolation and enable comparative analysis across studies.

5. Pharmaceutical properties of *Phyllanthus* genus

Phyllanthus species have been used and studied in decades. Their remarkable medicinal values such as antiviral, antioxidant, antidiabetic, anticancer and immunomodulatory properties cause scientists to establish many research of biological activities of constituents exist in these plants. Some distinctive characteristics of bioactive metabolites of the *Phyllanthus* genus were summarized.

5.1. Antiallergic Activity

Allergic reactions are primarily mediated by the release of histamine and other inflammatory mediators from mast cells. *Phyllanthus amarus* has demonstrated significant antiallergic properties by inhibiting these pathways. A study investigated the effects of *P. amarus* extract and its compounds on allergic response biomarkers, specifically β-hexosaminidase and histamine. The findings revealed that the extract effectively inhibited the release of these mediators from mast cells, suggesting its potential as a natural antiallergic agent (Abd Rani *et al*., 2021). Allergic reactions are initiated by allergen-specific CD4+ Th2 cells, leading to the production of IL-4, IL-5, and IL-13, which promote IgE synthesis (Akdis *et al*., 2005). Studies indicate that extracts of *Phyllanthus* species inhibit these pathways: *Phyllanthus amarus* extract reduced β-hexosaminidase release in RBL-2H3 cells with an IC_{50} of 22.5µg/mL (Vo *et al*., 2012), ethanolic extract of *Phyllanthus urinaria* inhibited mast cell degranulation in mice, reducing histamine levels by 41% (Nguyen *et al*., 2019).

5.2. Antioxidant Activity

Phyllanthus species are rich in polyphenolic compounds, which contribute to their significant antioxidant properties. These antioxidants play a crucial role in neutralizing free radicals, thereby preventing oxidative stress-related diseases. For instance, studies have demonstrated that extracts from *Phyllanthus emblica* exhibit potent antioxidant activity, attributed to its high content of vitamin C and other phenolic compounds. Hydroxyl-rich composition might be the reason for the remarkable antioxidant activities of methanol and aqueous extracts of *Phyllanthus* genus. Further studies stated that total phenolic was correlated with antioxidant activity. Hydromathnolic extract of *P. virgatus* exhibited antioxidant capacity in both DPPH scavenging (IC_{50} = 30.4μg/mL) and linoleic acid oxidation inhibiting (84%) method. *P. acidus*, *P. polyphyllus*, and *P. fraternus* showed significant hepatoprotective activity against acetaminophen, carbon tetrachloride, bromobenzene and thioacetamide, which are liver toxicity (Jain and Singhai, 2011; Jain *et al*., 2011; Rajkapoor *et al*., 2008; Gopi *et al*., 2010). Antioxidant level and other biochemical parameters were restored by these parts at the dose of 300mg/kg. Moreover, mitochondrial dysfunction in the liver which caused bay bromobenzene was relieved by oral administration of aqueous extracts of *P. fraternus* at the dose of 100mg/kg (Ramakrishna *et al*., 2012). Aqueous fraction of *P. amarus* was considered to reduce the damage of mitochondrial protein degradation, lipid peroxidation and mitochondrial DNA damage caused by Antimycin A and membrane damage of Hep3B cells caused by H_2O_2.

The antioxidant activity of members of *Phyllanthus genus* was also investigated. Nguyen Tien Toan and Nguyen Xuan Duy have shown that *Phyllanthus amarus* extract under the condition of ethanol 50% for 20 min at 60^{o}C with a ratio of material/solvent of 1/30 exhibited antioxidant activity via scavenging DPPH radical (Nguyen and Nguyen, 2014). Moreover, the extracts of hexane and methanol of *Phyllanthus amarus* Schum. Et Thonn has evidenced scavenging DPPH radicals at IC_{50} values of 60.2 and 21.9µg/ml, respectively (Nguyen *et al*., 2019). Notably, EtOAc extract of *Phyllanthus reticulatus* Poir. was found to be effective in scavenging DPPH radical at IC_{50} value of 4.7µg/ml (Nguyen *et al*., 2017).

Besides, the hepatoprotective effect of *Phyllanthus* species was also reported in different experiment models. Nguyen Ngoc Hanh and Tran Le Quan have shown that lignan, especially niranthin, from *P. niruri* L. was able to protect hepatic cells against GaIN/TNF-alpha-induced damage (Nguyen and Tran, 2004). Moreover, oral administration of Hepamarin derived from *P. amarus* (4g/kg) for 15 days exhibited protective effect up to 99.9% against CCL4-damaged liver cells in mouse and maintained ratio of GOT/GPT in a normal situation (Nguyen *et al*., 1996).

The high hydroxyl content in *Phyllanthus* contributes to its potent antioxidant properties: *P. virgatus* methanolic extract exhibited DPPH radical scavenging with an IC_{50} of 30.4µg/mL (Jain *et al*., 2011), aqueous extract of *P. amarus* significantly reduced lipid peroxidation and mitochondrial DNA damage in Hep3B cells at 100µg/mL (Ramakrishna *et al*., 2012). Several *Phyllanthus* species have been traditionally used to treat liver disorders. Recent studies have provided scientific evidence supporting their hepatoprotective effects. For instance, *Phyllanthus amarus* has been shown to protect against chemically induced liver damage in animal models, likely due to its antioxidant and anti-inflammatory properties (Bose Mazumdar Ghosh *et al*., 2022).

5.3. Antidiabetic Activity

The antidiabetic potential of *Phyllanthus* species has been explored in recent years. Studies have reported that extracts from these plants can modulate carbohydrate metabolism, enhance insulin sensitivity, and exhibit inhibitory activity against enzymes like α-amylase and α-glucosidase, which are involved in glucose metabolism. These findings support the traditional use of *Phyllanthus* species in managing diabetes. A wide range of *Phyllanthus* species traditionally employed for diabetes in many countries. Recent studies about the hypoglycemic effect of *Phyllanthus* plants were plentiful. Streptozotocin and alloxan-induced diabetic rats were chosen to evaluate the antidiabetic potential of *P. emblica, P. niruri, P. reticulatus, P. sellowianus, P. virgatus, and P. simplex* (Nain *et al*., 2012; Kumar *et al*., 2007; Hnatyszyn *et al*., 2002; Hashim *et al*., 2014; Shabeer *et al*., 2009). After oral administration of aqueous, methanol, and ethanol extracts of these plants in 21-45 days, the concentration of blood glucose was significantly reduced, and the effects of *P. sellowianus* and *P. simplex* were similar to the glibenclamide group (10mg/kg). Additionally, methanol fraction of *P. virgatus* seemed to inhibit the activity of *α*-amylase in the noncompetitive pattern with IC_{50} of 33.20 ± 0.556*μ*g/mL (Hashim *et al*., 2013). After being treated with aqueous extract of *P. niruri* through oral route for 28 days, the levels of LPO and malondialdehyde (MDA) were decreased while the concentrations of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) were increased. After being pretreated with the aqueous fraction of *P. sellowianus*, hemorheological parameters were improved. The aggregation and agglutination of red blood cells in large, globular form was observed (Buszniez *et al*., 2014). Methanolic extract of *P. virgatus* inhibited α-amylase in a noncompetitive manner (IC_{50} = 33.2μg/mL) (Hashim *et al*., 2013). In streptozotocin-induced diabetic rats, *P. sellowianus* extract reduced fasting blood glucose levels comparable to glibenclamide (10mg/kg) (Buszniez *et al*., 2014).

5.4. Anticancer Activity

Several *Phyllanthus* species have demonstrated anticancer properties in recent studies. The bioactive compounds present in these plants, such as lignans and flavonoids, have been found to induce apoptosis and inhibit proliferation in various cancer cell lines. For example, *Phyllanthus niruri* extracts have shown cytotoxic effects against liver and breast cancer cells, suggesting their potential as complementary therapies in oncology (Abdel-Sattar *et al*., 2023). Different extracts of the *Phyllanthus* plants have been assessed for anticancer effects and the related mechanisms. Chosen target cancer cell lines include NCI-H1703, MDA-MB-231, HeLa, 143B, PC-3, MCF-7, HepG2, A549, SKOV3, and HT-29. Considerably, their growth and other physiological activities were inhibited by *P. emblica, P. urinaria, P. polyphyllus, P. watsonii, and P. pulcher* (Rajkapoor *et al*., 2007; Tuchinda *et al*., 2008; Ngamkitidechakul *et al*., 2010; Zhao *et al*., 2015, Huang *et al*., 2014; Lee *et al*., 2011; Tang *et al*., 2010; Tang *et al*., 2013, Ramasamy *et al*., 2012; Ismail *et al*., 2012). Remarkably, *P. emblica* showed no toxicity toward normal cells (MRC5). By up-regulating Mitochondrial fission 1 protein and down-regulating optic atrophy type 1 and mitofusin, these extracts promoted fragmentation of DNA and dysfunction of mitochondria, which lead to the inhibition of cancer cell growth (Huang *et al*., 2014). These extracts also suppressed invasion, migration, and adhesion of cells as well. Ehrlich ascites carcinoma tumor model was used to evaluate the antitumor activity of *P. polyphyllus*. Oral administration of methanol extracts at the dose of 200mg/kg significantly reduced the tumor size. Besides, Hematological parameters, protein, packed cellular volume (PCV), and

antioxidant enzymes such as GPx, SOD, CAT và GST (Glutathione S-transferase) were effectively regulated as well. *P. urinaria* extract induced apoptosis in MCF-7 breast cancer cells through the mitochondrial pathway (IC_{50} = 21.3µg/mL) (Huang *et al*., 2014). Methanol extract of *P. polyphyllus* reduced tumor volume in Ehrlich ascites carcinoma models by 35% at 200mg/kg (Rajkapoor *et al*., 2007).

5.5. Antimicrobial and Antiviral Activities

The antimicrobial activity of *Phyllanthus* species has been extensively studied, with extracts showing inhibitory effects against a range of bacterial and fungal pathogens. These antimicrobial properties are attributed to the presence of bioactive compounds such as tannins, saponins, and flavonoids, which disrupt microbial cell walls and inhibit enzyme activity. The antiviral potential of *Phyllanthus* species has been a focal point of recent research. Extracts from these plants have shown inhibitory effects against various viruses, including hepatitis B and C viruses, human immunodeficiency virus (HIV), and herpes simplex virus (HSV). The mechanisms underlying these antiviral activities are believed to involve the inhibition of viral replication and modulation of host immune responses (Nisar *et al*., 2018). Several *Phyllanthus* species were reported to have strong antiviral potential such as anti-HIV, anti-HCV, anti-HSV, and anti-HCMV. The aqueous extract of *P. emblica* reduced viral load of HIV significantly at the dose of 400*µ*g/mL (Bothiraja *et al*., 2011). Aqueous extract of *P. sellowianus* inhibited DNA-polymerase and ribonuclease H (RNase H) activities of HIV-1 reverse transcriptase by IC_{50} values of 2.4 ± 0.8µg/mL and 5.9 ± 1.4µg/mL, respectively (Hnatyszyn *et al*., 1999). Additionally, methanol extract of *P. reticulatus* prevented the activity of RNase H by 99% at the dose of 50µg/mL (Tai *et al*., 2011). HCV-infected HuH7 cells were chosen to evaluate the anti-HCV ability of methanol extracts of *P. amarus*. The fraction suppressed the replication of HCV monocistronic replicon RNA and HCV H77S viral RNA without damaging host cells. Inhibiting HCV-NS3 protease enzyme and NS5B enzyme were suggested to be the main mechanism (Ravikumar *et al*., 2011). Aqueous extract of *P. emblica* significantly reduced HIV viral load at 400µg/mL (Bothiraja *et al*., 2011). Methanol extract of *P. reticulatus* inhibited HIV-1 reverse transcriptase RNase H activity by 99% at 50µg/mL (Tai *et al*., 2011).

5.6. Analgesic Activity

The extracts of *P. corcovadensis*, *P. niruri*, and *P. tenellus* caused significant reduction in writhing response induced by acetic acid, with ID_{50} values of 30, 19, and >30mg/kg, respectively. The late phase of formalin-induced pain could be relieved by *P. tenellus* with ID_{50} of 100mg/kg. Both phases of formalin-induced pain could be reduced by *P. corcovadensis* and *P. niruri* with ID_{50} values of 100 and 52mg/kg, respectively. The analgesic effects could not be antagonized by naloxone (Santos *et al*., 1999). In addition, intraperitoneal injection of hydroalcoholic extracts of *P. amarus*, *P. orbicularis*, and *P. fraternus* produced a notable analgesic activity by inhibiting acetic acid-induced abdominal constriction, capsaicin-induced neurogenic pain, and late phase of formalin-induced paw licking (Santos *et al*., 2000). Ethanol and aqueous extracts of *P. emblica* inhibited acetic acid-induced writhing response but failed in the tail immersion test (Perianayagam *et al*., 2004).

5.7. Anti-Inflammatory and Immunomodulatory Activities

Chronic inflammation is a hallmark of various allergic conditions. *Phyllanthus emblica* has been reported to exhibit anti-inflammatory effects by inhibiting the production of

nitric oxide (NO) and cyclooxygenase-2 (COX-2) enzymes in macrophage cells. This inhibition helps prevent excessive inflammatory responses, thereby alleviating symptoms associated with allergic reactions (Prananda *et al*., 2023). Furthermore, the immunomodulatory properties of these plants have been highlighted in studies demonstrating their ability to enhance immune system components, such as increasing levels of immunoglobulins and immune cells. Recently, various inflammatory models including Freund's complete adjuvant-induced arthritis, carrageenan-induced paw edema, and cotton pellet-induced granuloma were employed to evaluate the anti-inflammatory effects of *Phyllanthus*. After being treated with the aqueous extract of *P. amarus*, indexes of arthritis, joint diameter, and paw volume decreased and thresholds of mechanical hyperalgesia and nociceptive increased (Mali *et al*., 2011). Ethanol fraction of *P. simplex* improved the parameters of paw edema and granuloma and substantially inhibited nitric oxide (NO) production (Chouhan *et al*., 2011). Ethanol extracts of *P. urinaria* and *P. amarus* were proven to have inhibitory effects on the chemotaxis of neutrophils and monocytes with IC_{50} lower than 2.92μg/mL. Furthermore, phagocytic activity and CD18 expression of neutrophils and monocytes were downregulated (Jantan *et al*., 2014). Oral administration of *P. reticulatus* extract at the dose of 100mg/kg demonstrated a significant increase in phagocytic activity, the percentage of neutrophil adhesion, and white blood cell in albino mice (Kumar *et al*., 2014).

5.8. Hypotensive Activity

Aqueous extract of the leaves of *P. amarus* was proved to restrain both force and rate of myocardial contraction and to inhibit the intrinsic myogenic contraction of isolated rat portal vein (Amaechina *et al*., 2007). Aqueous part of *P. reticulatus* was effectively released total cholesterol, lipid profile, and oxidative stress in hypercholesterolemic albino rats after oral administered for 45 days at 250mg/kg (Maruthappan *et al*., 2010).

5.9. Wound Healing

Extracts of *P. emblica and P. niruri* posed wound healing effects. Proliferation of cells and cross-link of collagen in the full thickness excision wound could be promoted by the topical application of *P. emblica*. By up-regulation of IL-10 and down-regulation of TNF-α and IL-1β, extracts of P. emblica applied through oral route showed healing effects on NSAID-induced gastric ulcer (Chatterjee *et al*., 2011). After being treated with *P. niruri* at the dose of 200mg/kg, 98.8% of wounds could be recovered in the excision and incision wound models on the 16th day (Venkateshwarlu *et al*., 2012).

5.10. Antimalarial Activity

Malaria is a prevalent and deadly disease in many tropical and subtropical countries. Locals of these places especially Asian and African people used *Phyllanthus* as antimalarial agency. Plasmodium falciparum was suppressed by ethyl acetate fraction of *P. acidus* with IC_{50} of 9.37μg/mL, and the SI equals 4.88 for HEp-2 cells and 11.75 for Vero cells. Moreover, chloroquine-resistant *P. falciparum* was exhibited by *P. amarus* and *P. muellerianus* with IC_{50} values of 11.7 and 9.4μg/mL, respectively. *P. amarus* posed a protection effect on human RBCs damage caused by the virus (Appiah-Opong *et al*., 2011). The SI of *P. muellerianus* was higher than 5.3 for L-6 and MRC-5 cell lines (Zirihi *et al*., 2005; Ndjonka *et al*., 2012).

5. Conclusion

The *Phyllanthus* genus exhibits a wide array of biological activities, including antioxidant, antiviral, anticancer, antidiabetic, antimicrobial, anti-inflammatory, immunomodulatory, and hepatoprotective effects. These findings underscore the therapeutic potential of *Phyllanthus* species and support their traditional uses in various cultures. However, further clinical research is essential to confirm its safety and efficacy in human applications. Standardizing extraction and quantification methodologies will enhance reproducibility and facilitate drug development.

References

Abd Rani NZ, Lam KW, Jalil J, Mohamad HF, Mat Ali MS, Husain K (2021). Mechanistic studies of the antiallergic activity of *Phyllanthus amarus* Schum. & Thonn. and its compounds. *Molecules*, *26*(3), 695.

Abdel-Sattar OE, Allam RM, Al-Abd AM *et al.* (2023). Cytotoxic and chemomodulatory effects of *Phyllanthus niruri* in MCF-7 and MCF-7^{ADR} breast cancer cells. *Scientific Reports*, 13, 2683.

Akdis CA, Akdis M (2011). Mechanisms of allergen-specific immunotherapy. *Journal of Allergy and Clinical Immunology*, *127*(1), 18-27.

Akdis M, Blaser K, Akdis CA (2005). T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases. *Journal of Allergy and Clinical Immunology*, *116*(5), 961-968.

Amaechina FC, Omogbai EK (2007). Hypotensive effect of aqueous extract of the leaves of *Phyllanthus amarus* Schum and Thonn (Euphorbiaceae). *Acta Poloniae Pharmaceutica*, *64*(6), 547-552.

Appiah-Opong R, Nyarko AK, Dodoo D, Gyang FN, Koram KA, Ayisi NK (2011). Antiplasmodial activity of extracts of *Tridax procumbens* and *Phyllanthus amarus* in in vitro Plasmodium falciparum culture systems. *Ghana Medical Journal*, *45*(4), 143-150.

Arshad SH (2010). Does exposure to indoor allergens contribute to the development of asthma and allergy? *Current Allergy and Asthma Reports*, *10*(1), 49-55.

Awomukwu DAike, Nyananyo BL, Uka CJ, Okeke CU (2015). Identification of the genus *Phyllanthus* (Family Phyllanthaceae) in Southern Nigeria using comparative systematic morphological and anatomical studies of the vegetative organs. *Journal of Plant Sciences*. *3*(3), 137-149.

Bose Mazumdar Ghosh A, Banerjee A, Chattopadhyay S (2022). An insight into the potent medicinal plant *Phyllanthus amarus* Schum. and Thonn.. *Nucleus*, 65, 437-472.

Bothiraja C, Shinde MB, Rajalakshmi S, Pawar AP (2011). In vitro anti-HIV-type 1 and antioxidant activity of *Emblica officinalis*. *Research Journal of Pharmacy and Technology*, 2, 556-558.

Buszniez P, Di Sapio O, Riquelme B (2014). Effects of *Phyllanthus sellowianus* Müll Arg. extracts on the rheological properties of human erythrocytes. *Cell Biochemistry and Biophysics*, *70*(2), 1407-1416.

Chatterjee A, Chattopadhyay S, Bandyopadhyay SK (2011). Biphasic effect of *Phyllanthus emblica* L. extract on NSAID-induced ulcer: An antioxidative trail weaved with immunomodulatory effect. *Evidence-Based Complementary and Alternative Medicine*, 2011, 146808.

Chouhan HS, Singh SK (2011). Phytochemical analysis, antioxidant and anti-inflammatory activities of *Phyllanthus simplex*. *Journal of Ethnopharmacology*, *137*(3), 1337-1344.

Dierick BJH, van der Molen T, Flokstra-de Blok BMJ, Muraro A, Postma MJ, Kocks JWH, van Boven JFM (2020). Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. *Expert Review of Pharmacoeconomics and Outcomes Research*, *20*(5), 437-453.

Do TL (1997). Những cây thuốc và vị thuốc Việt Nam. NXB Y học, Hà Nội.

Doan MD, Nguyen HT, Nguyen DL (2018). Isolation and quantity determination of phyllanthin, hypophyllanthin from *Phyllanthus urinaria* L. by liquid chromatography- mass spectrometry (LC-MS/MS). *Journal of Science and Technology, University of Sciences, Hue University*, 13, 13-24.

Galli SJ, Tsai M, Piliponsky AM (2008). The development of allergic inflammation. *Nature*, *454*(7203), 445-454.

Gopi S, Setty OH (2010). Protective effect of *Phyllanthus fraternus* against bromobenzene induced mitochondrial dysfunction in rat liver mitochondria. *Food and Chemical Toxicology*, *48*(8-9), 2170-2175.

Hashim A, Khan MS, Ahmad S (2014). Alleviation of hyperglycemia and hyperlipidemia by *Phyllanthus virgatus* forst extract and its partially purified fraction in streptozotocin induced diabetic rats. *Excli Journal*, 13, 809-824.

Hashim A, Khan MS, Khan MS, Baig MH, Ahmad S (2013). Antioxidant and α -amylase inhibitory property of *Phyllanthus virgatus* L.: an in vitro and molecular interaction study. *BioMed Research International*, 2013:729393.

Hnatyszyn O, Broussalis A, Herrera G, Muschietti L, Coussio J, Martino V, Ferraro G, Font M, Monge A, Martínez-Irujo JJ, Sanromán M, Cuevas MT, Santiago E, Lasarte JJ (1999). Argentine plant extracts active against polymerase and ribonuclease H activities of HIV-1 reverse transcriptase. *Phytotherapy Research*, *13*(3), 206-209.

Hnatyszyn O, Miño J, Ferraro G, Acevedo C (2002). The hypoglycemic effect of *Phyllanthus sellowianus* fractions in streptozotocin-induced diabetic mice. *Phytomedicine*, *9*(6), 556-559.

Huang ST, Bi KW, Kuo HM, Lin TK, Liao PL, Wang PW, Chuang JH, Liou CW (2014). *Phyllanthus urinaria* induces mitochondrial dysfunction in human osteosarcoma 143B cells associated with modulation of mitochondrial fission/fusion proteins. *Mitochondrion*, 17, 22-33.

Ismail M, Bagalkotkar G, Iqbal S, Adamu HA (2012). Anticancer properties and phenolic contents of sequentially prepared extracts from different parts of selected medicinal plants indigenous to Malaysia. *Molecules*, *17*(5), 5745-5756.

Jain NK, Lodhi S, Jain A, Nahata A, Singhai AK (2011). Effects of *Phyllanthus acidus* (L.) Skeels fruit on carbon tetrachloride-induced acute oxidative damage in livers of rats and mice. *Journal of Chinese Integrative Medicine*, *9*(1), 49-56.

Jain NK, Singhai AK (2011). Protective effects of *Phyllanthus acidus* (L.) Skeels leaf extracts on acetaminophen and thioacetamide induced hepatic injuries in Wistar rats. *Asian Pacific Journal of Tropical Medicine*, *4*(6), 470-474.

Jantan I, Ilangkovan M, Yuandani, Mohamad HF (2014). Correlation between the major components of *Phyllanthus amarus* and *Phyllanthus urinaria* and their inhibitory effects on phagocytic activity of human neutrophils. *BMC Complementary Medicine and Therapies*, 14, 429.

Kay AB (2000). Overview of 'allergy and allergic diseases: with a view to the future'. *British Medical Bulletin*, *56*(4), 843-864.

Kumar S, Kumar D, Deshmukh RR, Lokhande PD, More SN, Rangari VD (2008). Antidiabetic potential of *Phyllanthus reticulatus* in alloxan-induced diabetic mice. *Fitoterapia*, *79*(1), 21-23.

Kumar S, Sharma S, Kumar D, Kumar K, Arya R (2014). Immunostimulant activity of *Phyllanthus reticulatus* Poir: a useful plant for infectious tropical diseases. *Asian Pacific Journal of Tropical Disease*, 4, S491-S495.

Lee SH, Jaganath IB, Wang SM, Sekaran SD (2011). Antimetastatic effects of *Phyllanthus* on human lung (A549) and breast (MCF-7) cancer cell lines. *PLoS One*, *6*(6), e20994.

Li XM, Brown L (2009). Efficacy and mechanisms of action of traditional Chinese medicines for treating asthma and allergy. *Journal of Allergy and Clinical Immunology*, *123*(2), 297-306.

Mali SM, Sinnathambi A, Kapase CU, Bodhankar SL, Mahadik KR (2011). Anti-arthritic activity of standardised extract of *Phyllanthus amarus* in Freund's complete adjuvant induced arthritis. *Biomedicine and Aging Pathology*, 1, 185-190.

Malone M, Kennedy TM (2017). Review: Side effects of some commonly used allergy medications (decongestants, anti-leukotriene agents, antihistamines, steroids, and zinc) and their safety in pregnancy. *International Journal of Allergy Medications*, *3*(1), 1-6.

Mao X, Wu LF, Guo HL, Chen WJ, Cui YP, Qi Q, Li S, Liang WY, Yang GH, Shao YY, Zhu D, She GM, You Y, Zhang LZ (2016). The Genus *Phyllanthus*: An Ethnopharmacological, Phytochemical, and Pharmacological Review. *Evidence-Based Complementary and Alternative Medicine*, 2016:7584952.

Maruthappan V, Shree KS (2010). Effects of *Phyllanthus reticulatus* on lipid profile and oxidative stress in hypercholesterolemic albino rats. *Indian Journal of Pharmacology*, *42*(6), 388-391.

Milián E, Díaz AM (2004). Allergy to house dust mites and asthma. *Puerto Rico Health Sciences Journal*, *23*(1), 47-57.

Nain P, Saini V, Sharma S, Nain J (2012). Antidiabetic and antioxidant potential of *Emblica officinalis* Gaertn. leaves extract in streptozotocin-induced type-2 diabetes mellitus (T2DM) rats. *Journal of Ethnopharmacology*, *142*(1), 65-71.

Ndjonka D, Bergmann B, Agyare C, Zimbres FM, Lüersen K, Hensel A, Wrenger C, Liebau E (2012). In vitro activity of extracts and isolated polyphenols from West African medicinal plants against *Plasmodium falciparum*. *Parasitology Research*, *111*(2), 827-834.

Ngamkitidechakul C, Jaijoy K, Hansakul P, Soonthornchareonnon N, Sireeratawong S (2010). Antitumour effects of *Phyllanthus emblica* L.: induction of cancer cell apoptosis and inhibition of in vivo tumour promotion and in vitro invasion of human cancer cells. *Phytotherapy Research*, *24*(9), 1405-1413.

Ngo VT, Nguyen KQC, Huynh NT, Lieu HMT (2009). Study of medicinal plants named Diep ha chau (*Phyllantus* spp.) Growing in South Vietnam Part I: Botanical Investigation of Medicinal Plants Named Diep ha chau, 14, 67-73.

Nguyen NH, Tran LQ (2004). Investigation of hepatoprotective activity of lignan from *Phyllanthus niruri* L. on hepatotoxicity model using D-GAIN/TNF-alpha. *Journal of Pharmacy*, 8, 10-11.

Nguyen PD, Nguyen VK, Nguyen DK, Dinh VH, Le VDT, Nguyen DK. Therapeutic effects of hepamarin preparation prepared from *Phyllanthus amarus* on mice with experimental hepatitis caused by carbon tetrachloride. *Journal of Practical Medicine*, 6, 4-8.

Nguyen TC, Nguyen CTT, Do TP, Vu TTP, Nguyen TN, Gilles T, Do TT (2017). The antioxidant and *in vitro* hepatoprotective activities of some chemical fractions from *Phyllanthus reticulates* Poir. plant. *Journal of Biotechnology*, 15, 251-258.

Nguyen TT, Nguyen XD (2014). Effect of extracting conditions on polyphenol content and antioxidant activity of Diep Ha Chau (*Phyllanthus amarus*) cultivated in Phu Yen. *Journal of Science and Development*, *12*(3), 412-421.

Nguyen TT, Pham NT, Nguyen NH (2004). Isolation and structure determination of alkaloid from the leaves of *Phyllanthus nirurii* L.. *CTU Journal of Science*, 2, 7-10.

Nguyen XTDT, Ly TD, Pham HN (2019). Identifying chemical components and antioxidation ability of *Phyllanthus amarus* Schum. Et Thonn. *Vietnam Trade and Industry Review*, 8, 433-438.

Nisar MF, He J, Ahmed A, Yang Y, Li M, Wan C (2018). Chemical components and biological activities of the genus *Phyllanthus*: A review of the recent literature. *Molecules*, *23*(10), 2567.

Ono SJ (2000). Molecular genetics of allergic diseases. *Annual Review of Immunology*, 18, 347-366.

Ouwehand AC (2007). Antiallergic effects of probiotics. *The Journal of Nutrition*, *137*(3 Suppl 2), 794S-7S.

Perianayagam JB, Sharma SK, Joseph A, Christina AJ (2004). Evaluation of anti-pyretic and analgesic activity of Emblica officinalis Gaertn. *Journal of Ethnopharmacology*, *95*(1), 83-85.

Prananda AT, Dalimunthe A, Harahap U, Simanjuntak Y, Peronika E, Karosekali NE, Hasibuan PAZ, Syahputra RA, Situmorang PC, Nurkolis F (2023). *Phyllanthus emblica*: a comprehensive review of its phytochemical composition and pharmacological properties. *Frontiers in Pharmacology*, 14, 1288618.

Rajkapoor B, Sankari M, Sumithra M, Anbu J, Harikrishnan N, Gobinath M, Suba V, Balaji R (2007). Antitumor and cytotoxic effects of *Phyllanthus polyphyllus* on Ehrlich ascites carcinoma and human cancer cell lines. *Bioscience, Biotechnology, and Biochemistry*, *71*(9), 2177-2183.

Rajkapoor B, Venugopal Y, Anbu J, Harikrishnan N, Gobinath M, Ravichandran V (2008). Protective effect of *Phyllanthus polyphyllus* on acetaminophen induced hepatotoxicity in rats. *Pakistan Journal of Pharmaceutical Sciences*, *21*(1), 57-62.

Ramakrishna V, Gopi S, Setty OH (2012). Protective effect of *Phyllanthus fraternus* against bromobenzene-induced mitochondrial dysfunction in rat kidney. *Chinese Journal of Natural Medicines*, 10, 328-333.

Ramasamy S, Abdul Wahab N, Zainal Abidin N, Manickam S, Zakaria Z (2012). Growth inhibition of human gynecologic and colon cancer cells by *Phyllanthus watsonii* through apoptosis induction. *PLoS One*, *7*(4), e34793.

Ravikumar YS, Ray U, Nandhitha M, Perween A, Raja Naika H, Khanna N, Das S (2011). Inhibition of hepatitis C virus replication by herbal extract: *Phyllanthus amarus* as potent natural source. *Virus Research*, *158*(1-2), 89-97.

Santos AR, De Campos RO, Miguel OG, Filho VC, Siani AC, Yunes RA, Calixto JB (2000). Antinociceptive properties of extracts of new species of plants of the genus *Phyllanthus* (Euphorbiaceae). *Journal of Ethnopharmacology*, *72*(1-2), 229-238.

Santos AR, Filho VC, Niero R, Viana AM, Moreno FN, Campos MM, Yunes RA, Calixto JB (1994). Analgesic effects of callus culture extracts from selected species of *Phyllanthus* in mice. *Journal of Pharmacy and Pharmacology*, *46*(9), 755-759.

Shabeer J, Srivastava RS, Singh SK (2009). Antidiabetic and antioxidant effect of various fractions of *Phyllanthus simplex* in alloxan diabetic rats. *Journal of Ethnopharmacology*, *124*(1), 34-38.

Tai BH, Nhut ND, Nhiem NX, Quang TH, Thanh Ngan NT, Thuy Luyen BT, Huong TT, Wilson J, Beutler JA, Ban NK, Cuong NM, Kim YH (2011). An evaluation of the RNase H inhibitory effects of Vietnamese medicinal plant extracts and natural compounds. *Pharmaceutical Biology*, *49*(10), 1046-1051.

Tang YQ, Jaganath I, Manikam R, Sekaran SD (2013). *Phyllanthus* suppresses prostate cancer cell, PC-3, proliferation and induces apoptosis through multiple signalling pathways (MAPKs, PI3K/Akt, NFκB, and hypoxia). *Evidence-Based Complementary and Alternative Medicine*, 2013, 609581.

Tang YQ, Jaganath IB, Sekaran SD (2010). *Phyllanthus* spp. induces selective growth inhibition of PC-3 and MeWo human cancer cells through modulation of cell cycle and induction of apoptosis. *PLoS One*, *5*(9), e12644.

Tran TH, Chu DT, Vu TA, Bui TBV, Chu VM (2018). Quantitative analysis of phyllanthin in *Phyllanthus amarus* L. using ultra-performance liquid chromatography with fluorescence detector. *Journal of Military Pharmaco-medicine*, 3, 26-31.

Tuchinda P, Kornsakulkarn J, Pohmakotr M, Kongsaeree P, Prabpai S, Yoosook C, Kasisit J, Napaswad C, Sophasan S, Reutrakul V (2008). Dichapetalin-type triterpenoids and lignans from the aerial parts of *Phyllanthus acutissima*. *Journal of Natural Products*, *71*(4), 655-663.

Venkateshwarlu G, Veliyath SK, Vijayabhaskar K, Harishbabu K, Malothu R, Sahoo S (2012). Wound healing activity of *Phyllanthus niruri* in albino wistar rats. *Asian Journal of Chemistry*, 24, 3929-3930.

Vo TS, Kim JA, Ngo DH, Kong CS, Kim SK (2012). Protective effect of chitosan oligosaccharides against FcεRI-mediated RBL-2H3 mast cell activation. *Process Biochemistry*, *47*(2), 327-330.

Vo TS, Ngo DH Kim SK (2012). Marine algae as a potential pharmaceutical source for anti-allergic therapeutics. *Process Biochemistry*, 47, 386-394.

Wan Saidin WA, Jantan I, Abdul Wahab SM, Jalil J, Mohd Said M, Yusoff SD and Husain K (2023). Pharmacological activities and mechanisms of action of hypophyllanthin: A review. *Frontiers in Pharmacology*, 13, 1070557.

Warren CM, Jiang J, Gupta RS (2020). Epidemiology and burden of food allergy. *Current Allergy and Asthma Reports*, *20*(2), 6.

Zhao HJ, Liu T, Mao X, Han SX, Liang RX, Hui LQ, Cao CY, You Y, Zhang LZ (2015). Fructus phyllanthi tannin fraction induces apoptosis and inhibits migration and invasion of human lung squamous carcinoma cells in vitro via MAPK/MMP pathways. *Acta Pharmacologica Sinica*, *36*(6), 758-768.

Zirihi GN, Mambu L, Guédé-Guina F, Bodo B, Grellier P (2005). In vitro antiplasmodial activity and cytotoxicity of 33 West African plants used for treatment of malaria. *Journal of Ethnopharmacology*, *98*(3), 281-285.