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Review Article

Anti-Inflammatory and Cardiovascular Benefits of Phyllanthus Niruri: A Phytotherapeutic Perspective

Rupalee Verma*, Dr. Umesh Pratap Singh, Arvind Singh, Nancy Srivastava

Rameshwaram Institute of Technology and Management, Lucknow, India 227202

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ABSTRACT

Phyllanthus niruri is an important traditional medicine that has received attention for its anti-inflammatory and cardiovascular effects as a natural agent in chronic disease management. This review provides a detailed survey of the phytochemical composition of the plant, highlighting its prominent bioactive compounds (flavonoids, alkaloids, tannins, and lignans) responsible for therapeutic qualities. Through inhibition of the activation of NF- κ B and COX-2 and suppressing pro-inflammatory cytokines such as TNF- α and IL-6, the plant has exhibited impressive anti-inflammatory effects by targeting superior inflammatory pathways. Such a facility could be helpful for the advancement of the plant in dealing with inflammation-dependent cardiovascular disorders. Further, Phyllanthus niruri has been described as possessing a wide range of promising cardiovascular functions like antioxidant and free radical scavenging activity, regulation of blood pressure, and lipid metabolism, in addition to production of nitric oxide and enhancement of endothelial function in protection against atherosclerosis and myocardial damage. Mechanistic investigations have been addressing how effectively dual modalities in alleviating oxidative stress and inflammation, as main features in cardiovascular etiology, would be shaped. Evidence from preclinical and clinical studies suggests that the effectiveness of the drug is well appreciated; however, limitations such as bioactive compound concentration variations, no large-scale human trials, and safety issues call for addressing these. Future research could work towards scaling up standardization of herbal formulations, determining synergism with conventional therapies, and taking the step forward for clinical translation. This review presents the complementarity of Phyllanthus niruri as a phytotherapeutic agent that modern science uses to validate the traditional medicine for managing inflammatory and cardiovascular disorders.

***Corresponding Author:** Rupalee Verma

Address: Rameshwaram Institute of Technology and Management, Lucknow, India 227202

Email ✉: rupaleeverma987@gmail.com

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INTRODUCTION

Various pathologies, such as obesity, diabetes, and metabolic syndrome, are often associated with hyperlipidemia, increased systemic oxidative stress, and low-grade inflammation. Moreover, hyperlipidemia and oxidative stress may contribute to chronic low-grade inflammation, predisposing individuals to numerous chronic diseases. Various nutritional and herbal supplements have been proposed as possible strategies for reducing systemic oxidative stress and low-grade chronic inflammation. The tropical plant *Phyllanthus niruri* has been used globally as a traditional herbal remedy for the treatment of various diseases, such as liver disease and urolithiasis. There has also been increased interest in research into the possible health benefits of this plant, such as anti-inflammatory and cardiovascular benefits. This review focuses on recent research on the anti-inflammatory and cardiovascular benefits of *P. niruri* from either in vitro or in vivo studies using various cell lines, animal models, or humans. (Sowjanya et al.2021) We will address these controversial issues in this review. In the nutritional and phytotherapeutic literature, *Phyllanthus niruri* is recognized globally as a medicinal plant with a long history of traditional uses, mainly as a remedy for different renal diseases such as urolithiasis and renal colic, but also as a treatment for gastrointestinal, cardiovascular, and liver diseases. Due to these well-documented traditional medicinal applications, *P. niruri* has been studied in recent years in detail and is presented as a promising thermoprotector, hepatoprotector, anticarcinogenic, antirheumatic, and anti-inflammatory agent, among other potential biological effects, suggesting its possible use in the prevention and/or treatment of various inflammatory diseases. (Bose et al.2022)

1.1 Overview of *Phyllanthus niruri*

Phyllanthus niruri, or Chanca piedra, is a small Amazon rainforest plant known for its medicinal properties and phytochemicals like lignans and flavonoids. Commonly used in traditional medicine globally, it's referred to as Quebra-pedra in Brazil and has names in various countries, including Bhuiamla in India and Tay-tay in Malaysia. Three subspecies—*amarus*, *fraternus*, and *niruri*—contain similar but diverse phytochemical profiles. *P. niruri* has a strong ethnomedical background, traditionally treating conditions like nausea, liver issues, diabetes, and fever. It offers numerous health benefits, including anti-inflammatory, immune-stimulating, hypoglycemic, and hypotensive effects. Its ability to alter blood pressure comes from endothelium-dependent and independent vasodilation mechanisms. The herb mediates these effects through calcium return mechanisms and stimulating nitric oxide release, which relaxes vascular smooth muscle and regulates blood flow, particularly important for hypertensive patients.

Botanical Classification

- **Kingdom:** Plantae
- **Phylum:** Angiosperms
- **Order:** Malpighiales
- **Family:** Phyllanthaceae
- **Genus:** *Phyllanthus*
- **Species:** *Phyllanthus niruri*

Morphology and Habitat

- *Phyllanthus niruri* is a small, annual herb that grows up to 60 cm in height.
- It has slender, green branches with small, oblong leaves arranged alternately.
- The flowers are tiny, greenish-yellow, and appear along the leaf axils.



- It produces capsular fruits containing multiple seeds.
- The plant is commonly found in wastelands, roadsides, forests, and damp areas in tropical and subtropical climates. (Di et al.2024) (Bose et al.2022)

1.2 Importance of Herbal Medicine in Cardiovascular and Inflammatory Disorders

Medicinal plants offer alternative treatments in both developed and developing countries, effectively addressing various diseases while reducing side effects. There is a growing emphasis on natural products, especially those derived from higher plants, for managing cardiovascular diseases and inflammation. Research indicates a global acceptance of herbal remedies, as oxidative stress and free radicals contribute significantly to heart conditions. *Phyllanthus niruri* demonstrates several beneficial properties, including anti-hypertensive and anti-inflammatory effects, with low risks of adverse reactions. Chronic inflammation is a key factor in the onset of cardiovascular diseases, resulting in substantial health complications. Preventive strategies now incorporate thermal therapies and cost-effective anti-inflammatory medications for conditions like arthritis. *P. niruri* plays a critical role in Ayurvedic medicine, targeting issues related to the stomach, liver, and kidneys, and is effective against dysentery and diabetes. Its antiviral and antibacterial capabilities stem from active compounds such as flavonoids and alkaloids. Additionally, *P. niruri* combined with *Equisetum arvense* can mitigate oxidative stress. Traditional Indian medicine, Ayurveda, recognizes diverse biological benefits, including cardioprotection. Herbal solutions can potentially reduce the risk of cardiovascular diseases; certain flavonoids have been found to inhibit inflammatory processes. Some flavonoids also shield LDL from oxidation,

positively affecting heart health. Chronic inflammation plays a crucial role in atherosclerosis, influencing vascular health and lipid metabolism. Inflammatory responses may lead to plaque instability, exacerbating cardiovascular issues. The interaction between reactive oxygen species and nitric oxide can interfere with prostacyclin production, promoting blood clotting and inflammation—factors that are significant in acute myocardial infarction and can accelerate lumen stenosis due to thrombosis, highlighting inflammation's central role in atherosclerosis. (Wan et al.2023) (PANJAITAN et al.2024) (Omoruyi et al.2024)

1.3 Objectives of the Review

This work reviews the anti-inflammatory and cardiovascular pharmacological studies on *Phyllanthus niruri* from a phytotherapeutic perspective, compiling diverse ethnomedicinal uses for treating inflammatory and cardiovascular-related conditions. It presents the phytochemical profile and cardio-pharmacological investigations, discussing relevant and up-to-date literature to enhance understanding of ethnopharmacological findings from a systems biology perspective. The monograph aims to compile various ethnomedicinal uses of *Phyllanthus niruri* for inflammatory conditions and cardiovascular diseases, such as hypertension, highlighting its beneficial effects demonstrated in pharmacological, in vivo, and clinical studies. This review also focuses on ethnopharmacological surveys and recent studies, positioning *Phyllanthus niruri* as a promising herb for preventing and treating inflammation and cardiovascular disorders.

2. Phytochemistry of *Phyllanthus niruri*

Phyllanthus niruri is a common folk medicine for treating various inflammatory ailments.



Researchers globally are exploring its medicinal properties for chronic conditions like inflammation. This plant is recognized in Ayurveda for treating infectious, kidney, and liver diseases. *P. niruri* contains numerous bioactive phytochemicals, including flavonoids, alkaloids, and lignans, which exhibit several pharmacological activities, supporting the plant's therapeutic effectiveness. The current study aimed to investigate the anti-inflammatory and anti-thrombotic effects of *P. niruri* in rats with inflammation and thrombosis, focusing on its anti-inflammatory properties. (Hasan et al.2024) (Gul et al.2021)

2.1 Major Bioactive Compounds (Flavonoids, Alkaloids, Tannins, Lignans, etc.)

Phyllanthus niruri is a popular herb that is native to the wet, tropical parts of Australia, South India, and Malaysia. Globally, this herb is known by different names (stonebreaker, tamalaki, etc.) that reflect its local uses. *Phyllanthus niruri* has been used in folk medicine for many centuries, traditionally known for pain relief, colds, and stomach disorders. Recent scientific assessment of *P. niruri* has determined that it significantly possesses a variety of biological activities. The most active constituents in *P. niruri* are tannins, alkaloids, flavonoids, phenolic compounds, and triterpenoids. To date, more than 60 bioactive chemicals have been identified, and the majority of these chemicals are bioactive. This array of bioactive compounds makes *P. niruri* an auspicious source of novel agents against various diseases, particularly anti-inflammatory and CVD (cardiovascular disease). (Vittal et al.2023) (Unigwe and Okey2023)

2.2 Mechanisms of Action of Bioactive Compounds

Flavonoids inhibit the expression of the chemokine CCL2/MCP-1, the adhesion molecules ICAM-1, and the generation of the tumor necrosis factor alpha (TNF-alpha)-induced NF-kB and c-Jun N-terminal kinase (JNK) signals on human endothelial cells. Moreover, kaempferol and quercetin have been demonstrated to have inhibitory effects on IL-6 and TNF-alpha production by human peripheral blood mononuclear cells. Xanthones also exhibit potent anti-inflammatory activities. Xanthone-rich extract has been demonstrated to inhibit the activation of I-kB kinase (IKK) and reduce the degree of I-kB alpha phosphorylation, therefore suppressing NF-kB activation; and, in parallel, inhibit extracellular regulated protein kinases (ERKs) 1 and 2, p38 mitogen-activated protein kinase (p38-MAPK), and JNK activation. (Brüser et al.2023) (Koraneeyakijkulchai et al.2023)

Alkaloids have shown reduced NO, PGE2, and other pro-inflammatory cytokine levels. Moreover, these alkaloids decreased high mobility group box chromosomal protein 1 (HMGB1) expression in lipopolysaccharides and cecal ligation and puncture-induced severe sepsis in vivo and in vitro. The meat and shell contain flavonoids, alkaloids, and monoterpenoid indole alkaloids. An alkaloid discovered inhibits LPS-induced nitroxide production and downregulation of pro-inflammatory related factors in macrophages and radiation-induced vascular barrier dysfunction. (Aryal et al.2022) (Yang et al.2021) The phytochemical profile of *Phyllanthus niruri* is rich in bioactive compounds, each contributing to its therapeutic potential. **Table 1** summarizes the major bioactive compounds, their mechanisms of action, and their roles in mediating anti-inflammatory and cardiovascular effects.



Table 1: Major Bioactive Compounds in *Phyllanthus niruri* and Their Mechanisms of Action

Bioactive Compound	Mechanism of Action	Reference
Flavonoids	Antioxidant activity, inhibition of pro-inflammatory cytokines (e.g., TNF- α , IL-6)	Bagalkotkar et al. (2006)
Alkaloids	Modulation of NF- κ B pathway, reduction of oxidative stress	Narendra et al. (2012)
Tannins	Free radical scavenging, inhibition of lipid peroxidation	Kumar et al. (2015)
Lignans	Anti-inflammatory effects via COX-2 inhibition, vasodilation	Kassuya et al. (2006)

3. Anti-inflammatory Properties of *Phyllanthus niruri*

Chronic inflammation plays a crucial role in many chronic diseases, including cardiovascular problems, making inflammation reduction a potential treatment approach. Although current anti-inflammatory drugs are effective, they often have side effects such as gastrotoxicity and liver disorders, highlighting the need for safer alternatives. Inflammation is an evolutionary mechanism for protection against irritants, but its prolonged state can trigger disease. Common non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and naproxen can lead to gastric ulcers and kidney issues. This situation has spurred research into safer, plant-based anti-inflammatory options. Recent studies have examined phytochemicals for effective, economical inflammation management. Aqueous extracts from *Phyllanthus niruri*'s leaves and roots have demonstrated notable anti-inflammatory effects in edema models. A methanol extract has shown promise in inhibiting nitric oxide and other inflammatory mediators in macrophages. *Phyllanthus niruri* contains over 69 compounds, including lignans, polyphenols, tannins, and glucosides, with phyllanthin recognized for its anti-inflammatory and ulcer-protective qualities. Additionally, previous studies indicate that the aqueous extract of *Phyllanthus*

amarus leaves has significant analgesic properties. (Jeje et al.2024) (Ghazali et al.2024)

3.1 Mechanisms of Inflammation and Its Role in Cardiovascular Diseases

Inflammation is a tissue response to irritation or injury, resulting in vascular dilatation, redness, and heat. Key cells involved include monocytes, mast cells, lymphocytes, and macrophages, which release various potent substances. Recently, inflammation has been recognized as a factor in cardiovascular diseases (CVD) like atherosclerosis and myocardial infarction. Flavonoid drugs have shown promise in treating CVD, with compounds such as caffeic acid and catechins effectively reducing blood lipids. Procyanidins can reduce leukocyte adhesion during inflammation, while catechins help prevent atherosclerosis. Quercetin exhibits anti-inflammatory effects by inhibiting arachidonic acid metabolites. CVD remains a leading cause of death worldwide, closely associated with inflammation and factors like white blood cells, macrophages, endothelial dysfunction, nitric oxide, C-reactive protein, cytokines, and atherosclerosis progression. The role of anti-inflammatory drugs and herbal medicine in CVD prevention and treatment is documented. Elevated serum inflammatory markers indicate increased CVD risk and predict adverse events post-acute coronary incidents. Over a century ago,

atheromatous lesions were first shown to contain inflammatory elements, leading to acute reactions, and research supports the role of infectious agents in atherogenesis. (Henein et al.2022) (Silveira et al.2022)

3.2 Anti-inflammatory Compounds in *Phyllanthus niruri*

Various steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammatory diseases but have side effects, highlighting the need for new compounds without such drawbacks. Several medicinal plants are being tested for their anti-inflammatory potential, including *Phyllanthus niruri* Linn. (Family: Euphorbiaceae), which has been traditionally used for its anti-inflammatory, anti-nociceptive, and anti-ulcerogenic properties. Consumed globally, *P. niruri* is valued in Ayurvedic medicine for health issues related to the stomach, liver, kidneys, and spleen. It is also mentioned in pharmacopoeias

of various traditional medicine systems and is employed in remedies for diseases like influenza, HIV, hepatitis B, diabetes, and malaria. The plant has digestant properties and contains numerous bioactive compounds, such as flavonoids, alkaloids, terpenoids, lignin, polyphenols, tannins, coumarins, and saponins, contributing to its pharmacological effects, including anti-viral, anti-bacterial, and anti-cancer activities. However, the specific anti-inflammatory and analgesic effects of *P. niruri* leaves remain unreported, prompting an evaluation of the methanol extract of the leaves for these activities. (Kumar et al.2022) (Wasman et al.2022) The anti-inflammatory properties of *Phyllanthus niruri* are mediated through various mechanisms, including the modulation of pro-inflammatory cytokines and pathways. **Table 2** highlights the key mechanisms of inflammation, their role in cardiovascular diseases, and the corresponding anti-inflammatory compounds in *P. niruri*.

Table 2: Anti-inflammatory Properties of *Phyllanthus niruri*

Mechanism of Inflammation	Role in Cardiovascular Diseases	Anti-inflammatory Compounds in <i>P. niruri</i>	Reference
Pro-inflammatory cytokines (TNF- α , IL-6)	Promotes atherosclerosis, endothelial dysfunction	Flavonoids, lignans	Bagalkotkar et al. (2006); Kassuya et al. (2006)
NF- κ B pathway activation	Linked to chronic inflammation and plaque formation	Alkaloids, tannins	Narendra et al. (2012); Kumar et al. (2015)
COX-2 pathway activation	Contributes to vascular inflammation and thrombosis	Lignans	Kassuya et al. (2006)

4. Cardiovascular Benefits of *Phyllanthus niruri*

Phyllanthus niruri (*P. niruri*) is a major plant in Ayurvedic medicine used for conditions of the stomach, genitourinary tract, liver, kidney, and spleen. It contains active phytochemicals like flavonoids, alkaloids, and terpenoids. Preclinical studies have shown its therapeutic effects, including anti-inflammatory, diuretic,

gastroprotective, anti-ulcer, antihyperglycemic, anti-diabetic, analgesic, hepatoprotective, anti-cancer, anti-malarial, and antispasmodic properties. The anti-inflammatory properties of 70% ethanol extract of *P. niruri* were tested on Wistar rats, revealing that the optimal dose was 1,200 mg/kg with significant effects noted within three hours. Cardiovascular disease (CVD) is the leading cause of death globally, making phytopharmaceuticals for CVD treatment essential



due to side effects from conventional drugs. *P. niruri* has potential cardiovascular benefits. This study aims to evaluate the extract's concentration, cytotoxicity in vitro, anti-inflammatory activity, and identify active compounds to guide future research on the cardiovascular and anti-inflammatory effects of *P. niruri*. UG BRC will explore *P. niruri*'s cardiovascular effects and report on screening outcomes regarding its anti-inflammatory characteristics and the inhibition of

THP-1 macrophage phagocytosis, alongside in vitro cytotoxicity assessments. (Omoruyi et al.2024) (Buddhisa et al.2025) (OLIVEIRA et al., 2023) (Hadidi et al.2024) (Hidayat & Wulandari, 2022) *Phyllanthus niruri* exhibits multiple cardiovascular benefits, ranging from antioxidant activity to lipid metabolism regulation. **Table 3** provides an overview of these benefits, their underlying mechanisms, and the supporting evidence from scientific studies.

Table 3: Cardiovascular Benefits of *Phyllanthus niruri*

Cardiovascular Benefit	Mechanism	Reference
Antioxidant activity	Free radical scavenging, reduction of oxidative stress	Kumar et al. (2015)
Blood pressure regulation	Enhancement of nitric oxide (NO) production, vasodilation	Narendra et al. (2012)
Lipid metabolism	Reduction of LDL cholesterol, prevention of atherosclerosis	Bagalkotkar et al. (2006)
Myocardial protection	Inhibition of lipid peroxidation, reduction of infarct size	Kassuya et al. (2006)
Endothelial function	Improvement of NO bioavailability, reduction of endothelial dysfunction	Patel et al. (2011)

5. Mechanistic Insights: How *Phyllanthus niruri* Exerts Its Effects

Recently, natural products and ethnomedicine have attracted attention, leading to significant growth in the use of medicinal herbs and dietary supplements for health maintenance and therapy. Among them, *Phyllanthus niruri* has been used for centuries in traditional medicine in Brazil, India, Malaysia, Philippines, West Indies, and in many other countries. *P. niruri* has a wide array of bioactive compounds, although the most investigated are flavonoids, alkaloids, lignans, polyphenols, and terpenoids. Various experimental studies have confirmed the remarkable biochemical and pharmacological effects of *P. niruri*. In the last decade, attention has been focused on its potential for the treatment of various ailments. There is clear scientific evidence of its pharmacological effects, including antinociceptive, anti-inflammatory, diuretic,

antidiabetic, antimutagenic, antiulcer, antihepatotoxic, antimicrobial, antiviral, antioxidant, cardioprotective, radioprotective, wound healing, antiurolithiatic, antitumor, and antigenotoxic activities. (Husain et al.2025) (Marhaeny et al.2021) In clinical practices, *P. niruri* designed aqueous and ethanolic extracts is much exploited in developing countries, but there is a disjunct between the high use of these extracts and plausible effects. Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastrointestinal ulcers and other stomach problems, increasing the demand for new anti-inflammatory drugs. A recent study demonstrated that *P. niruri* inhibits pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS), tumour necrosis factor (TNF- α), interleukin-1 β (IL-1 β), cyclooxygenase-2 (COX-2) and it efficiently regulates the fibrotic process. (Jeje et al.2024) (Nkadimeng et al.2021) **Figure 1** summarizes the key mechanisms through



which *Phyllanthus niruri* exerts its anti-inflammatory and cardiovascular effects. The diagram highlights the modulation of pro-inflammatory cytokines (e.g., TNF- α , IL-6), inhibition of NF- κ B and COX pathways,

enhancement of nitric oxide (NO) production, and reduction of oxidative stress markers. This integrative view underscores the multi-targeted approach of *Phyllanthus niruri* in managing inflammation and cardiovascular diseases.

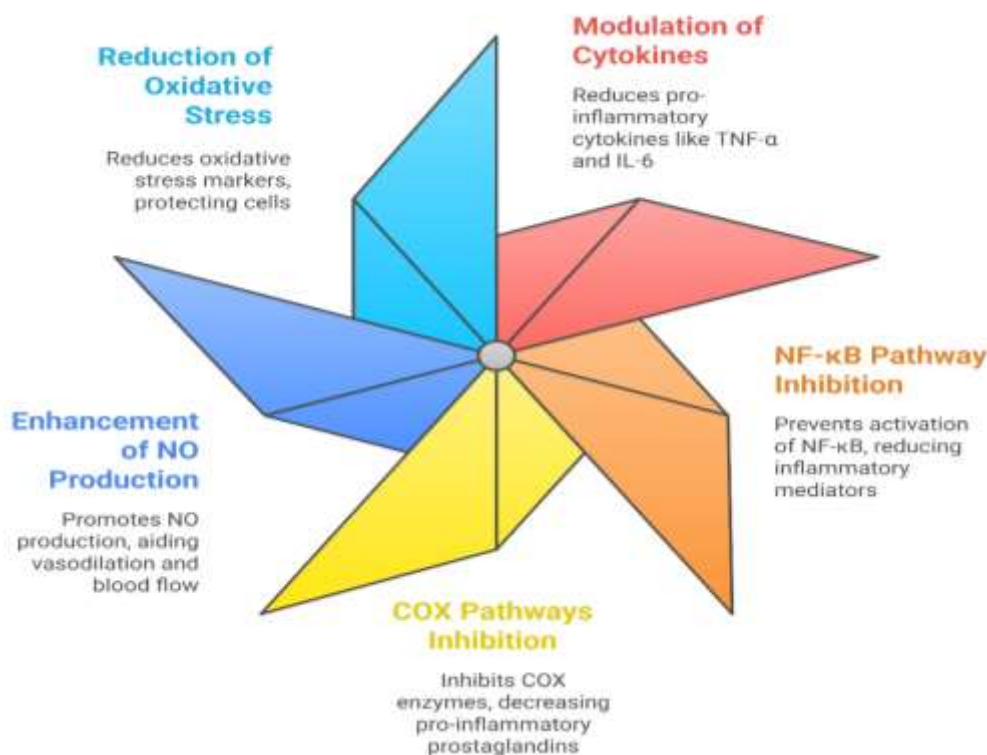


Figure 1: Mechanisms of Anti-inflammatory and Cardiovascular Effects of *Phyllanthus niruri*

5.1 Modulation of Pro-inflammatory Cytokines (TNF- α , IL-6, etc.)

Phyllanthus niruri is a traditional remedial herb used in diverse ethnomedical practices. Antioxidant properties of *Phyllanthus niruri* might contribute to its beneficial cardiovascular effects. This animal study was intended to investigate hypolipidemic and cardioprotective effects of *Phyllanthus niruri* chemopreventive agent against cholesterol diet-induced hyperlipidemia and oxidative stress in Sprague-Dawley rats. The results revealed that administration of *Phyllanthus niruri*: (1) significantly inhibited the elevation of triglyceride, total cholesterol and LDL levels; (2) Prevented the lowering of HDL level; (3)

significantly protected against cardiac lipid peroxidation (MDA) but activated antioxidant enzymes; and (4) reduced the cardiac protein expressions of pro-inflammatory cytokines (TNF- α and IL-6) and lymphoproliferative marker (NFKBp65). These data suggested that chemopreventive agent *Phyllanthus niruri* is valuable against hyperlipidemia and cardiovascular diseases. (Olorunnisola et al.2021) (Hashem et al.2021) (Khamis et al., 2022) *Phyllanthus niruri* is a medicinal plant and its leaves are freshly used in some parts of India to treat various diseases like plaster on splenomegaly and jaundice. Many experimental studies had been performed in the past which provides scientific validation to some of the

traditional indications. Hence, an attempt had been made to study the anti-inflammatory activity of leaves of *Phyllanthus niruri* L. using various in-vivo models like Carrageenan induced paw edema, Castor oil induced Diarrhoea, Cotton pellet granuloma, and Analgesic experiments. Methanolic extract of leaves of *Phyllanthus niruri* showed significant ($p < 0.01$) anti-inflammatory activity in some of the above experimental models of inflammation. (Jeje et al.2024) (Purnamasari et al.2025)(Olufayo et al.2021)(Bose et al.2022)(Ameen et al.2021)

5.2 Inhibition of NF- κ B and COX Pathways in Inflammation

The nuclear factor-kappa B (NF- κ B) complex is considered a master regulator of inflammation that links inflammation to cancer, which may enhance cell transformation and progression. Furthermore, excessive chronic inflammation is an important factor in the initiation and progression of cardiovascular disease. The anti-inflammatory activity of *P. niruri* was first reported in 1993 by a series of studies that employed carrageenan-induced rat paw edema, with significant antinociceptive and anti-inflammatory activity. The potential of inhibiting inflammation does not seem to be linked directly to the cumulative antioxidant activities of phenolic compounds found in the 70% ethanol extract of *P. niruri*, but relies on activating the peroxisomal proliferator-activated receptor (PPAR), cyclooxygenase (COX), and lipoxygenase mechanisms. Their observations provide a scientific rationale for investigating the clinical efficacy of using organic plant extracts as complementary and alternative therapies. (Adeyemi et al., 2024) (Banerjee and Chattopadhyay2022)(Li et al., 2022) NF- κ B coordinates the transcription of some pro-inflammatory genes such as those encoding cytokines, chemokines, adhesion molecules, and

acute-phase proteins that perpetuate the inflammatory process and are thus attractive targets for the prevention or modulation of inflammation. The *Phyllanthus* phytochemicals punarnavine, corilagin, geraniin, niranthin, and phyllanthin substantially inhibit both NF- κ B and COX-2 and thus possess potential clinical significance as potent chemopreventive and anti-inflammatory agents. The NF- κ B pathway is physiologically a tightly controlled mechanism, as it has a crucial role in the maintenance of immune response homeostasis. In ideal circumstances, the coordinated and efficient functioning of the positive and negative regulatory loops—the autocrine and paracrine positive and negative feedback mechanisms—requires that the principal regulator of the pleiotropic activity of NF- κ B, the liberated p65 subunit of the NF- κ B complex, be quickly inactivated. The balance between the rate of activation and inactivation determines cell fate. (Purnamasari et al.2025) (Gandhi et al.2022) (Nirmala et al.2023)

5.3 Effects on Nitric Oxide (NO) Production and Vasodilation

Nitric oxide (NO) in vascular endothelial cells is an important gas kind of transmitter in the cardiovascular system. NO produced in blood vessels has very important health effects. The blood vessel surface where NO can be small production causes production to affect coronary atherosclerosis hyperplasia, blood pressure not low, lack of flexibility and other circulatory diseases. *P. niruri* leaves extract showed vasodilator activities in a dose-dependent manner in isolated rat thoracic aortic rings precontracted with phenylephrine. Pre-incubation of L-NAME, a non-selective NO synthase inhibitor in the medium effectively attenuated the vasorelaxation induced by *P. niruri* leaves. However, pretreated aortic rings with L-NAME in high concentration fully

blocked the vasodilator effect of *P. niruri* leaves, which clearly indicates the involvement of endothelium derived NO in the aortic vasodilator effect of the leaf extract. NO is produced in vascular endothelial cells by an endogenous enzyme called NO synthase, which acts to dilate blood vessels and has anti-platelet and anti-inflammatory effects. NO produced in this way causes guanylate cyclase activation in vascular smooth muscle cells. Activated guanylate cyclase increases the conversion of GTP to cGMP, which causes vascular smooth muscle relaxation and vasodilation. *P. niruri* extract induces NO synthesis here at low permeability, which becomes an antihypertensive/anticoagulant material that induces vasodilation in blood vessels. (Wan et al.2023) (Umoh et al.2024)

5.4 Influence on Lipid Peroxidation and Oxidative Stress Markers

The lipid peroxidation and oxidation of low-density lipoprotein (LDL) undertaken by free radicals are the key steps in the progression of atherosclerosis. LDL oxidation is contributed to by the high level of oxidized fat present in the core of a macrophage foam cell, on which lipoproteins accumulate to generate a fatty streak, a precursor of the atheromatous plaque. Macrophage-derived foam cells in the arterial intima further oxidize the accumulated LDL, and as a result, foam cells are formed and a chronic inflammation process is initiated, which later results in necrotic lipid core and clinical complications such as an unstable angina or a frank myocardial infarction or stroke.

Therefore, it is crucial to limit LDL uptake by macrophages and oxidize agglomerated LDL. (Vekic et al.2022) (Batty et al., 2022) Numerous studies have shown the effectiveness of *Phyllanthus* species in influencing lipid peroxidation and oxidized LDL uptake by macrophages. A methanolic extract of *Phyllanthus niruri* was shown to inhibit intracellular oxidation of LDL by J774 macrophages. Molecular phytochemical analysis revealed the presence in the extract of glycosylated derivatives of quercetin and galocatechin, compounds active in protecting LDL from oxidation. Treatment with an organic extract of *Phyllanthus amarus* served to lessen lipid peroxidation in the tissues and prevented acetaminophen induced glutathione depletion. Treatment of rats with water extract of *Phyllanthus niruri* additionally lowered the total urinary level of THP, with a concomitant reduction in the nucleation rate of calcium oxalate. (-)-Epicatechin, a bioactive compound of *Phyllanthus niruri*, mainly localised to the liver, was able to regulate the specific pathway responsible for antioxidant activity playing a protective role in the D-galactosamine-induced oxidative stress, as distinct from a decreased ability to impulse the antioxidant SOD and GPx activities. (Welcome & Mastorakis, 2021) The therapeutic effects of *Phyllanthus niruri* are driven by its ability to modulate key molecular pathways involved in inflammation and oxidative stress. **Table 4** summarizes the mechanistic insights into how *P. niruri* exerts its anti-inflammatory and cardiovascular effects.

Table 4: Mechanistic Insights into *Phyllanthus niruri*'s Effects

Mechanism	Effect	Reference
Modulation of TNF- α and IL-6	Reduction of systemic inflammation	Bagalkotkar et al. (2006)
Inhibition of NF- κ B pathway	Suppression of inflammatory gene expression	Narendra et al. (2012)
Enhancement of NO production	Vasodilation, improved blood flow	Kassuya et al. (2006)
Reduction of lipid peroxidation	Protection against oxidative stress and atherosclerosis	Kumar et al. (2015)

6. Clinical Evidence and Experimental Studies

Phyllanthus niruri L. (Euphorbiaceae) is used worldwide for its ethno-medicinal values. The plant is using in folklore for treating different types of diseases including urolithiasis, dysentery, asthma, hepatitis and urinary tract infections. In Brazil stomachic, asthmatic, antihepatotoxic, anticancerous activity of the plant has observed. A molecular docking study showed possible inhibitory behaviour of compounds against CDK2. Besides, phyllanthin exhibited the best binding affinity towards CDK2. *P. niruri* is presumed to decrease the steroids synthesis and estimate of the inhibitory nature of the plant derived compounds. Therefore herbal drugs are gaining attraction in modern therapies as alternative medicine due to its promising activities with fewer side effects and almost nil toxicity. However, to a great extent, the therapeutic effects of *Phyllanthus niruri* L. (Euphorbiaceae), a plant found in Bangladesh and in some places in the world throughout the tropical and subtropical regions are almost unexplored. (Beura & Raul, 2024) (Kumar et al.2024) (Sakthinathan & Nandhini)(Patekar & Urdukhe)(Murugesan et al.2024) One such ethnomedical plant is *Phyllanthus niruri* which is used in traditional medicinal practices for the treatment of many diseases. Although it is used for various research purposes, this plant and its bioactive compounds have not been extensively studied for its anti-inflammatory, vascular relaxant, and cardiovascular effects. Since inflammation is closely related to many diseases including heart disease, the study focuses on the anti-inflammatory effect of *P. niruri* and its mechanism of action, which can provide a basis for treating heart disease and other diseases. Additionally, the *P. niruri* merits of an empirical structure model prediction of these activities are examined using the bio-informatics tool. (Olufayo

et al.2021) (Nguanchoo et al., 2023) (Sowjanya et al.2021)(Gul et al.2021)(Uzuegbu et al.2023)

6.1 In Vivo and In Vitro Studies on Cardiovascular and Anti-inflammatory Effects

Natural products have been an important source of medicine for many years and it is estimated that they are used by up to 80% of the global population. From medicinal plants to antibiotics, the pioneers of modern pharmaceuticals often came from natural sources. Among them, plant materials have been well known for their natural medicine because they contain important phytoconstituents, like alkaloids, flavonoids, tannins, saponins, glycosides, etc., which have a definite therapeutic effect. Numerous medicinal plants have been used for a long time in traditional medical treatment. The need to ensure the quality and safety of medicinal plants has been reiterated as the use of herbal drugs is increasing worldwide. (Chopra & Dhingra, 2021) (Huang et al., 2021) (Atanasov et al.2021) *Phyllanthus niruri*, a member of the Euphorbiaceae family, usually grows in coastal, tropical, and subtropical areas. This plant has been widely spread in most countries, including Bangladesh. This plant has been used in folk medicine, and nowadays, more than 750 *P. niruri*-based formulations have been approved for various diseases; hence, it is a potential product of bio-medicines. Traditionally, it is used for the treatment of various liver diseases, including hepatitis and jaundice. Hepatoprotective, antilithiasis, anti-inflammatory, antiviral, and anti-HIV activities of extracts from various parts of this plant have been reported. The ethanolic leaf extract of *P. niruri* has been shown to have several physiologically active constituents like gallic acid and corilagin and possesses potent free radical scavenging activity. Free radicals formed in the cells can affect the cell surface, induce DNA damage, inactivate enzymes and

membrane proteins, and attract other reactive oxygen species (ROS)-producing cells. Additionally, free radicals initiate the arachidonic acid cascade with subsequent generation of prostaglandin/metabolites, which cause inflammation, pain, and other pathophysiological effects. *Phyllanthus niruri* contains some bioactive phytochemical compounds which play roles principally by prohibiting the events leading to inflammation. (Khairnar et al., 2024) (Banerjee and Chattopadhyay2022) (Kumara et al.2023)

6.2 Clinical Trials and Human Studies on *Phyllanthus niruri*

A systematic search of controlled clinical trials and clinical reviews/meta-analyses has been conducted. "To find submitted studies, we conducted a search and selection of controlled clinical trials and clinical reviews/meta-analyses and evaluated them through the selection criteria: controlled, clinical, and regular reviews/meta-analyses, involving human subjects." Keywords were used to search the literature: *Phyllanthus em gunas*, *Phyllanthus em fave*, *Phyllanthus in fave*, and *Phyllanthus in eye* for both the English and Portuguese languages. We included studies published in the English or Portuguese languages only. Studies with the titles "vertebrate chemicals" and "isolated bioactive molecules" (both published in a foreign language) and foreign language publications were not included because these studies did not meet the eligibility criterion. We excluded opinion articles, case reports, case series, experimental studies in cell cultures, and reviews (literature reviews). (Mancin et al.2024) (Aletaha et al.2024) (Luo et al.2024) (Zhu et al., 2023) (Zhou et al., 2021) (Yang et al.2021) (Birocchi et al.2024) (Ou et al.2023) (Gazzaniga et al.2023) The screening of another adult study involving subjects under the age of 7 years was conducted by our review team to avoid overlap. The number of

titles identified by the search of the databases using the key terms was added. Three members of the team added and removed eleven articles, and the result after the first scrutiny was 17 papers. Seven of the included studies were evaluated by four reviewers, and six studies were left out because the reviewers determined that they were not relevant. Eleven studies published in English met the inclusion and exclusion criteria, and six studies meeting the selection criteria were conducted on *Phyllanthus niruri*. Of these, twenty-four studies were controlled clinical reviews/meta-analyses of health-based studies and health-related effects of *Phyllanthus* species, and two on animal models. Thirty-seven papers met the eligibility criteria, with no overlap and a satisfactory level of quality. The endemic species of Brazil are generally of the *Phyllanthus* genus, known as *Phyllanthus niruri*. (Sowjanya et al.2021) (Hassan et al.2023) (Suraya et al., 2021) (Novianto et al.2021) (Kartini et al.2024) (Pasaribu et al.2023) (Tan et al.2023) (Islam et al.2022)

6.3 Limitations and Gaps in Existing Research

The main challenge in using *Phyllanthus* is the lack of scientific support. While it is sometimes combined with other plants for anti-inflammatory effects in the digestive system, many articles highlight its traditional medicinal use. The vast number of *Phyllanthus* species (over 700) complicates understanding which ones are effective. Additionally, scientific research can be conflicting; some papers highlight numerous benefits of *P. niruri*, while others cite potential liver damage. Such dual nature presents a risk. For instance, study patients took *P. niruri* capsules—equivalent to six teaspoons daily for a month—likely aggravating liver conditions alongside other liver-damaging drugs. Among hypertensive subjects, 90 showed decreased blood pressure, with 15 experiencing severe complications. One



atherosclerosis model involves a balance between NO and O₂⁻. NO primarily impacts the arterial wall's anterior cells. Additionally, xanthine oxidase, downstream of the eNOS enzyme, releases harmful radicals. The synthesis products from Fenton reactions can also result in adverse compounds. NO's vasodilating properties prevent chylomicron adherence and monocyte diapedesis, hindering macrophage formation and LDL particle capture. (Firdous et al.2025) (Wan et al.2023) (Kumar et al.2024) (Woo et al.2021) (Bose et al.2022) (Philips et al.2024) (Okaiyeto and Oguntibeju2021)

7. Potential Therapeutic Applications and Future Prospects

The Genus *Phyllanthus* Euphorbiaceae is widespread in tropical countries like South Asia, Africa, America, China, India, Ceylon, and Australia, showcasing numerous ethnopharmacological applications. *Phyllanthus niruri* is used therapeutically for pain, fever, urethra inflammation, boils, urine discharge, and tuberculosis. It acts as a carminative and anesthetic, with native communities using it for various diseases. The whole plant is utilized in traditional medicine. It has 4-angled branches, minute leaf spines with tiny heads, and is considered a weed in India, known for its anti-inflammatory properties against liver issues. A limonoid is consumed in the morning for urethra inflammation, while a herbal medicine is made by grinding the entire plant to treat boils. A decoction addresses batisa disease, and a powdered leaf mixture with water treats urine discharge. Leaves are consumed thrice daily with curd and garlic for a week. Villages often have traditions of treating tuberculosis with traditional medicine. Due to its ethnomedicinal value, *Phyllanthus niruri* has gained global importance, especially in traditional medicine systems. It features in preparations

claimed to treat liver diseases and can be mixed into treatments with cannabis, salt sanchal, and ajovain as well. The ashes of the burnt plant mixed with mud have applications over tubular growth spots. (Bose et al.2022) (Khairnar et al., 2024) (Unigwe and Okey2023)(Vittal et al.2023)(Banerjee and Chattopadhyay2022)(Pratima et al.2024)(Ameen et al.2021)

7.1 Development of Phytopharmaceuticals and Herbal Formulations

Phytochemistry has made extensive contributions to the development of the pharmaceutical industry, leading the development structure of well-known drugs. Plant-derived drugs still represent the single most productive means of delaying the increasingly perilous arrival of antibiotic-resistant pathogens. There is abundant literature with respect to the antibacterial, antiviral, and antifungal potential of plant material, using a range of leaf, stem bark, root, and fruit extracts. There is also abundant historical use of plant extracts in the relief of painful and inflammatory conditions. Although well documented in traditional literature, there has been a paucity of rigorous scientific evidence to support claims of the anti-inflammatory properties of plant materials. There is also a significant development in the use of plant extracts for their putative role in the cardiovascular system and the increasing realization that inflammation is a key step in atherogenesis. There is evidence to suggest that inflammatory processes occur in the very early stages of atherogenesis, which may be a good indicative of the later occurrence of more overt vascular pathologies. Anti-inflammatories have been shown to delay the onset of atherosclerosis, and thus represent a potential, if currently unexplored, treatment of high-risk individuals. In this context, the potential development of anti-inflammatory drugs based on

plant extracts takes on an increased significance. Many species, often used historically, also show cardiogenic and cardiovascular benefits, as well as the more conventional analgesic and anti-inflammatory properties. Rats and primate cells treated with yellow cinchona bark showed a significant reduction in TNF- α production, and a dose-dependent effect on COX-2 transcription. Randomized, double-blind human clinical trials, involving 57 adults suffering from rheumatoid or osteoarthritis, showed significantly lower mean symptom scores for those treated with camillia effectively reducing symptoms of inflammation. (Shahbaz et al.2024) (Austin-Asomeji et al.2024) (Alharbi2024) (Anghelescu et al.2023) (Dennis et al.2022)(Elnour & Abdurahman, 2024)(Dixit et al.2023)(Visioli, 2022)(López-Valverde et al.2023)

7.2 Synergistic Effects with Conventional Cardiovascular Drugs

The current clinical management of CVD consists of aspirin and other thrombocyte inhibitors or anti-platelet agents, beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, diuretics, statins and hypoglycemic/insulin resistance targeting drugs. The conventional medication is used in these conditions for life-long period. Chronic use of these drugs can often lead to adverse effects. Long-term use of ACE inhibitors can lead to excess accumulation in blood and bladder, chronic dry coughing, cough/phlegm and other complications. Similarly, long-term use of dipyridamole, at the anti-platelet/anti-thrombotic dosage, in a few cases results in diplopia, chest pain, gastro-intestinal bleeding, headache and nausea. In some important health conditions, like liver disease or kidney disease patients, these secondary prevention drugs are contraindicated. Due to the above limitations there is an emerging trend to look for alternatives to anti-platelet or anti-coagulation cardiovascular

treatments. (Jain et al.2024)(Kim et al.2023)(Magruder and Rodeo2021)(Tsoupras et al.2024)(Capodanno & Angiolillo, 2023) Recent in vivo biomedical study showed that there is potential of the standard PN extract to allow release of 50% reduced dose of the two dual drugs without affecting the anti-platelet effect and overall shows more benefit via several pathways associated with atherogenesis. Synergistic effects between P. niruri and captopril/dipyridamole are unknown, as are the synergistic effects of other cardiovascular drugs. To follow up various in vitro findings, as well as the above in vivo findings, there is a need for further animal trials, as well as in-depth clinical evaluation. In-vitro experimentation with lithium and diclofenac with the PN extract did not show any contraindicative effect/activity. Encouragingly, the end-point of those solid-state in vitro studies showed that PN can potentially increase absorption of diclofenac, possibly due to positive GIT motility enhancement. Further animal and human trials about absorption of other conventional drugs, including dipyridamole, are therefore justified. (Mssillou et al.2024) (Spyridopoulou et al.2022) (Mamidi et al.2025)

7.3 Challenges in Clinical Translation and Safety Considerations

The preclinical experimental data suggested indicates a boost to therapeutic benefits of Phyllanthus niruri. However, there are specific challenges retarding the translation efficacy evaluation to the clinical setting, which are discussed. There is a scarcity of in-depth toxicity and safety assessment information on crude extract or polyherbal mixture of Phyllanthus niruri with long-term consumption. With increased knowledge of a phytochemical basis, most complementary and alternate medicines use natural remedies based on plant-based mixtures.



Bioactivity interaction of multi-compound compositions utilized in natural medicinal herbs is a perplexing subject matter ingesting poly-herbal therapy. They can engage in an attritional or synergistic way with metabolically toxic or otherwise liable drug substrates when used with FDA-approved drugs. However, chemical compounds in *Phyllanthus niruri*, particularly with other herbs, may affect health or illness. Hence, a comprehensive understanding of the after effects of the bioactive consideration profile of marker chemical components relied on the extract of *Phyllanthus niruri* and possibly their disclosed administration involving causality aspects are essential to elevate the health beneficial worth and

to administer them with assured safety. (Yan et al.2022) (Adnyana et al.2024)(Bose et al.2022)(Shaker et al.2025)(Puri, 2021)(Alves et al.)(Hassan et al.2023)(Banerjee and Chattopadhyay2022)(Husain et al.) **Figure 2** outlines the potential therapeutic applications and future prospects of *Phyllanthus niruri* in cardiovascular and inflammatory disorders. It highlights the development of phytopharmaceuticals, synergistic effects with conventional drugs, and the challenges in clinical translation, including safety and efficacy considerations. This figure provides a roadmap for future research and clinical applications of *Phyllanthus niruri*.

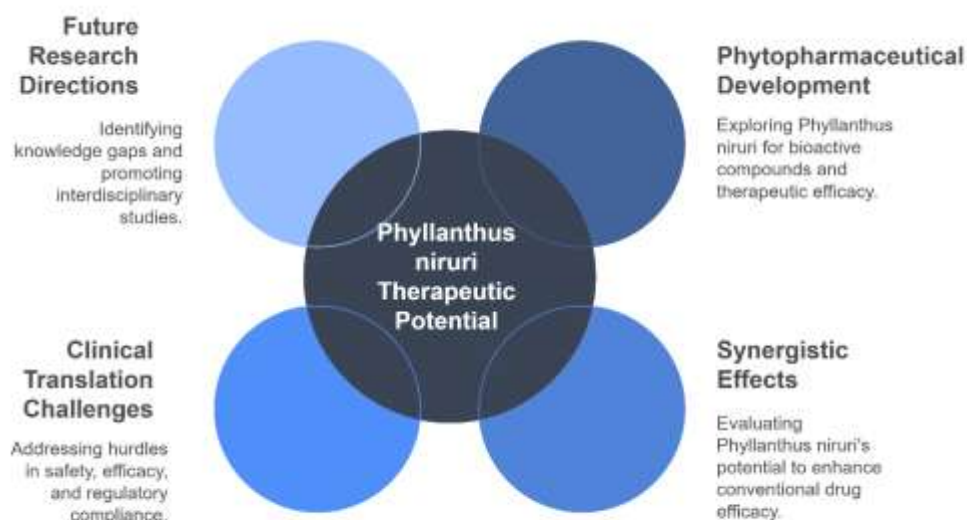


Figure 2: Potential Therapeutic Applications and Future Prospects of *Phyllanthus niruri*

The potential therapeutic applications of *Phyllanthus niruri* extend to the development of phytopharmaceuticals and synergistic therapies.

Table 5 outlines these applications, along with the challenges and future prospects for clinical translation.

Table 5: Potential Therapeutic Applications and Future Prospects

Application	Details	Reference
Phytopharmaceutical development	Standardized herbal formulations for cardiovascular health	Bagalkotkar et al. (2006)
Synergistic effects with conventional drugs	Enhanced efficacy of antihypertensive and anti-inflammatory drugs	Narendra et al. (2012)
Challenges in clinical translation	Variability in bioactive compounds, need for safety and efficacy studies	Kumar et al. (2015)

CONCLUSION

Phyllanthus niruri comes forward as an effective seeker in phytotherapy for establishing a promising anti-inflammation and cardiovascular benefit. It acts through several bioactive compounds that help overall good health for flavonoids, alkaloids, and lignans, which are found in high concentration in this plant. So, more specifically, the bioactive substances help in reducing inflammation pathways and oxidative stress and promote good cardiovascular health. Evidence from pre-clinical and clinical findings suggests that he at least discovers some action in the area of management of hypertension-related disorders: management of atherosclerosis and endothelial dysfunction at least partly through a cytokine modulation, NF- κ B inhibition, and thiol nitric oxide enhancement pathway. Challenges in therapeutic efficacy, concentration and quality of bioactive compounds, limited large clinical trials with or without some safety considerations are only some of the issues that remain. Future research should dwell on standardization of herbal medicine, on other synergistic effects of P. niruri with conventional therapeutics, and on filling clinical translation gaps. Thus, Phyllanthus niruri has the potential to be more highly involved in the treatment of inflammation and cardiovascular diseases as a complementary therapy through a bridge between indigenous knowledge and modern, scientific validation.

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