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Review Article

A review on the potential therapeutic effect of *Phyllanthus niruri* on Obesity and its related complications

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Abstract: *Phyllanthus niruri* L. (Phyllanthaceae), commonly known as Bhui Amla, is used as a traditional medicine in the Asian region. This review provides an overview of the therapeutic potential of *P. niruri* in the management of obesity, dyslipidemia, diabetes, hepatic disorders, chronic kidney disease (CKD), and inflammation. *P. niruri* plays a crucial role in obesity and hyperlipidemia by reducing body weight, visceral fat accumulation, serum cholesterol, triglycerides, low-density lipoprotein levels, and insulin resistance. On the contrary, it improves an individual's antioxidant status and lipid profile. Additionally, improved renal biomarkers, suppression of inflammatory biomarkers, and reduced fibrosis are signs of the renoprotective effects of *Phyllanthus niruri.* Furthermore, *P. niruri* demonstrates hepatoprotective and antifibrotic properties. Lowering liver enzyme levels, improving lipid metabolism, reducing inflammatory cytokines, and restoring normal hepatic architecture across various models of liver injury are signs of hepatoprotective and antifibrotic effects. Also show anti-inflammatory activities such as inhibition of edema formation, suppression of pro-inflammatory cytokines, and modulation of oxidative stress pathways. Clinical studies further support its safety and efficacy, particularly in liver diseases.

Keywords: *Phyllanthus niruri,* obesity and dyslipidemia, diabetes, hepato-protective, reno-protective

1. Introduction

Phyllanthus niruri L., in the genus *Phyllanthus* and family *Phyllanthaceae*, is a widely distributed tropical plant commonly found in coastal areas. This plant is found in Texas, Mexico, Central America, and vast regions of South America. It is also distributed in Africa, Asia, Australia, and Oceania, including wastelands and other areas. In Spanish, it is commonly known as chanca piedra. [1]. *Phyllanthus niruri* is a terminal herbaceous plant, typically 30- 60 cm tall, with a characteristic phyllanthoid branching pattern in which various branchlets

and leaf-like, compound leaves develop due to the quick abscission of leaves on the main stem. The main stem is smooth, cylindrical (terete), and hairless (glabrous)**,** approximately 1–2.5 mm in diameter. The stem and its branches are light green to reddish in color [2].

The crude extract of the whole plant or its Herbal Brews as a tea (Standard traditional dosage range is 1-2 grams) has been used in traditional medicine[3]. *Phyllanthus niruri* has been widely used in traditional, complementary, and integrative medicine (TCIM) to treat digestive problems, liver, kidney, and urinary conditions [3].

In Ayurveda, *Phyllanthus niruri* is known as "bhumi amla" [4]. Worldwide, it has been widely used in traditional, complementary, and integrative medicine (TCIM) systems to treat a range of medical conditions, including digestive problems and liver, kidney, and urinary conditions [3]. Traditionally, it has been used as a diuretic and antilithic agent, which aids in dissolving kidney stones and provides protection from urinary calculi [4,5]. In ancient India, this plant has been used to treat jaundice, hepatitis, fever, spleen disorders, and liver inflammation; in traditional Chinese medicine, it has been used as a diuretic, to support liver health, and to promote detoxification [3].

Phyllanthus niruri exhibits pharmacological actions to reduce fatty liver disease, including liver cirrhosis, diabetes mellitus, obesity, and dyslipidemia [4]. In Ayurveda, juice or powder from *Phyllanthus niruri* is used to treat viral infections and reduce bile production [6].

In traditional Malay medicine, *Phyllanthus niruri* is also used to manage diabetes, fever, wound healing, tissue repair, postpartum recovery, and gastrointestinal problems, including antiulcer effects. In Africa, specifically in Nigeria, Ghana, and Congo, it is used against fevers, infections, and malaria [3, 6,7].

2. Methodology

This review was conducted to evaluate the therapeutic effects of *Phyllanthus niruri* on obesity and dyslipidemia, diabetes, hepatic disorders, chronic kidney disease, and inflammation. This comprehensive literature review covers 10 years (2015-2025) of relevant articles, using online databases such as PubMed, Scopus, Google Scholar, ScienceDirect, and Web of Science. Keywords such as "*Phyllanthus niruri*," "obesity," "dyslipidemia," "diabetes," "chronic kidney disease," "renal protection," "hepatic fibrosis," "hepatoprotective," "inflammation," "antioxidant," and "clinical trial" were used while searching for relevant articles.

This review article uses a table format to organize all the extracted data, such as study design, experimental model, dosage, treatment duration, biomarkers assessed, molecular targets, histopathological findings, and major therapeutic outcomes, to ease reading & skimming of the selected relevant articles and uses EndNote software for referencing.

3. Role of *Phyllanthus niruri* in Obesity and Dyslipidemia

Obesity is a chronic, complex disease characterized by the accumulation of excessive body fat that has a detrimental effect on health, creating a massive global public health and economic crisis. Obesity is measured and expressed as Body Mass Index (BMI), where BMI> 25kg/m^2 is usually considered overweight, and BMI ≥ 30 kg/m^2 is defined as obesity [8]. However, obesity is associated with an imbalance in cholesterol pathways,

including low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, as well as triglycerides, leading to dyslipidemia. Abnormal lipid levels in the blood can be associated with an increased risk of cardiovascular disease. Dyslipidemia is generally divided into two types: primary and secondary. Primary dyslipidemia is caused by genetic mutations that affect lipid metabolism, whereas secondary dyslipidemia is acquired, with obesity or diabetes among the causes [9]. Nowadays, millions of individuals worldwide suffer from dyslipidemia, a public health issue that increases the risk of cardiovascular disease, the world's leading cause of mortality. Genetic and environmental variables influence the prevalence of dyslipidemia, which varies by geography, age, sex, and ethnicity [10].

Research has shown that in 2022, over 890 million adults were living with obesity, and more than 2.6 billion adults were obese. Statistics show that since 1975, the prevalence of obesity is increasing day by day, and this forecast implies that by 2035, nearly 1.9 billion adults and by 2050, around 60% of adults will be affected by obesity, making it a global health issue [11].

Obesity is a complicated and multifaceted disorder that can be caused by a variety of risk factors that are linked to metabolic and environmental variables, genetic predisposition, and genetic problems such as increased consumption of high-calorie & processed foods, less physical activity due to socioeconomic issues & urban living, and stress and sleep disturbances related to weight gain or appetite. Furthermore, long-term stress may trigger hormonal pathways that encourage the storage of fat [10].

The central nervous system (CNS) plays a significant role in maintaining & regulation body weight, specifically the hypothalamus, which integrates signals about hunger and energy resources. The fat-cell hormone leptin travels through the bloodstream and signals the hypothalamus to reduce appetite, whereas insulin, ghrelin, and peptide YY stimulate appetite and increase energy storage as fat. Adipose tissue produces leptin, which connects to the brain through a network known as the adipose-CNS axis [12].

Genetic mutations affecting LEP (encoding leptin) or LEPR (encoding the leptin receptor) cause uncontrolled appetite and early-onset obesity. Insulin resistance generally occurs in obesity and impairs glucose metabolism, promoting further fat accumulation. Of the two forms, monogenic obesity is rare but severe, due to mutations in a single gene (LEP, LEPR, MC4R); however, polygenic obesity is the most common and can arise from many genes. Genes like *FTO, PPARG, APOE*, and *PPARA* can contribute a small factor to this risk [12] [13]. More than 200 genetic variants have been associated with obesity by genome-wide association studies, but they collectively account for only a small percentage of total heritability [14].

Peripheral insulin resistance and chronic low-grade inflammation in obesity result from defective adipose tissue function, leading to the production of pro-inflammatory cytokines and abnormalities in adipokines, particularly due to excess visceral fat accumulation [15]. In the context of free fatty acids (FFA), there is an increase in their circulating levels and their uptake by the liver due to the inability of insulin to decrease lipolysis [16]. The central features of obesity-associated lipid abnormalities include excessive production of very large numbers of Very-Low-Density Lipoprotein (VLDL) particles with high triglyceride content, abnormalities in

lipid clearance, low HDL cholesterol, and the production of small, dense LDL particles. Deficiency of insulin due to obesity is aggravated by fat inflammation, and FFA is linked with lipotoxicity in muscles and the liver [17].

Reduced clearance and increased secretion of triglyceride-rich lipoproteins, as well as excessive VLDL secretion, are associated with high triglyceride levels. High VLDL, through cholesteryl ester transfer protein, also leads to low HDL-cholesterol (HDL-C) and the generation of small, dense LDL, which represents a greater risk of developing atheromas or ather [18]. Insulin usually inhibits adipose tissue lipolysis and suppresses VLDL secretion from the liver. This leads to insulin resistance due to suppression, which is especially reflected in the strong augmentation of FFA flux to the liver [16]. This increases VLDL secretion and de novo lipogenesis by the liver. In the context of LDL and oxidized lipoproteins, these accumulate pathologically in aortic walls, leading to the recruitment of inflammatory cells, including macrophages and/or vascular lymphocytes, and to immune rejection by activating the expression of VCAM -1 and/or ICAM-1. Atherosclerosis results from dyslipidemia exacerbated by the inflammatory response, and from dyslipidemia associated with the pathophysiology of increased endothelial dysfunction and plaque formation, as revealed by molecular research. Systemic insulin resistance is exacerbated by inflammation of the adipose tissue and hepatic lipid secretion, and the patterns of dyslipidemia are exacerbated by FFA Flux [19].

Orlistat, phentermine, topiramate, naltrexone, bupropion, and GLP-1 receptor agonists (semaglutide, liraglutide, tirzepatide, etc.) are some of the commercially available medications for obesity. However, studies in animal models (rats) demonstrate improved lipid profiles, decreased visceral fat, and improved glucose management, suggesting relevance to obesity-related metabolic dysfunction, which is why researchers are becoming interested in *P. niuri*. Plant extracts may have anti-obesity properties since they can inhibit pancreatic lipase, the same enzyme that orlistat targets, *in vitro. Phyllanthus niruri* may improve metabolic indices and reduce insulin resistance, according to studies in rats. According to certain ingestion studies, it is safe for people at the levels examined.

Al Zarzour et al. reported that in the HFD-induced male Sprague Dawley rat model, an 8-week Phyllanthus niruri diet consistently decreases body and organ weights [20]. The lipid profile TC, TG, ALT, AST, LDL, HDL, glucose, and leptin levels significantly decreased due to the *Phyllanthus niruri* treatment. The histopathological study reported that adipocyte size decreased with reduced inflammation [20]. Al Zarzour et al. showed that in HFD-induced male Sprague Dawley rats, a 50% methanolic extract of *Phyllanthus niruri* at 1000mg/kg body weight for 4 weeks of treatment increased adiponectin levels [21]. The pro-inflammatory cytokines (TNF-α, IL-6, RBP4, Vaspin, Progranulin) were decreased. The histopathological study of hepatic micro- and macrosteatosis and fibrosis levels showed significant decreases [21]. *Phyllanthus niruri* treatment also reduced microvessel growth and endothelial cells. Transporters such as PPARγ and SLC10A2, as well as collagen-1α levels, were decreased [21]. Balkrishna et al. used an Ayurvedic prescription medicine, Livogrit (extracts of *Boerhavia diffusa* L., *Phyllanthus niruri*, and *Solanum nigrum* L.), to see its hepatoprotective effect [22] on HepG2 spheroids and

rat primary hepatocytes. After the *Phyllanthus niruri* treatment, there was a reduction in lipid accumulation, AST, ROS, and inflammation levels. Treatment also improved lipolysis and mitochondrial potential, as well as stress-related genes (FGF21, FXR, CHOP, CXCL5) [22].

Hashem et al. studied male albino rats fed an HFD and treated with Phyllanthus niruri at 250 mg/kg body weight for 105 days. After treatment, ALT, AST, ALP, and VLDL levels significantly decreased, while HDL, albumin, and the A/G ratio decreased appropriately [23]. Serum C3 levels decreased, and blood glucose, insulin, HOMA-IR, and HOMA-beta levels also decreased. Microsteatosis, inflammation, and necrotic hepatocytes were also reduced [23]. Naik et al. stated that aspartame (ASP) was administered to female Swiss albino mice at 40 mg/kg body weight per day by oral gavage for 30 and 60 days [24]. After the treatment, all parameters decreased. Body weight and organ weights decreased; lipid profiles, ASP, TGs, ALP, AST, and LDH levels decreased. The ROS level of oxidative stress also decreased [24]. You et al. studied the effect of *Phyllanthus niruri* treatment (200 mg/kg body weight) in diethylnitrosamine (DEN)- induced male Wistar albino rats for 14 weeks [25]. Body weight, organ weight, liver weight & biomarkers of oxidative stress (8-OHdG & TBARS) decreased after treatment. The neutralizing antioxidants, such as SOD, CAT, GPx, GR, and GSH levels, increased, while the overall lipid profile (ALT, AST, ALP, TC, TGs), GGT, and LDH levels decreased [25]. Ezzat et al. demonstrated that CCl4 was administered to male Wistar rats at 1 mL/kg for 4 h. After administering *Phyllanthus niruri*, liver function LDH, ALP, TB, and AST levels, and triglycerides TP, TC, and TGs levels decreased. The oxidative reactive species (MDA, ROS, GSH & SOD) were measured, and they were significantly decreased. As a result, *Phyllanthus niruri* treatment inhibited the levels of NF-κB, TNF-α, IL-6, IL-8, IL-10, and iNOS [26]. Bharati et al. studied the effect of *P. niruri* in STZ-induced male Wistar rats and hypertensive rats at 600 mg/kg/day for 28 days [27]. When the *Phyllanthus niruri* treatment was administered, the levels of TGs, SGOT, and cholesterol significantly decreased, and pancreatic islet damage also decreased significantly. The treatment also showed overall improvements in body weight and metabolic function [27]. As a result of improved metabolic function and pancreatic and β-cell protection, blood glucose and MABP levels were reduced, according to their study [27]. Mediani et al. studied STZ-induced male Sprague Dawley rats at 250 and 500 mg/kg body weight for 4 weeks [28]. When the *Phyllanthus niruri* treatment was administered to the rat, the lipid profile- TGs, TC, LDL levels, and HDL levels- was reduced. The fasting blood glucose levels decreased significantly [28]. Also, there were improvements in glycolysis and gluconeogenesis, the TCA cycle, ketone body synthesis, and hypoaurine metabolism [28]. Giribabu et al. observed STZ-induced male Wistar rats at 200 and 400 mg/kg body weight for 28 days [29]. When *Phyllanthus niruri* treatment was administered, weight loss was prevented. Lipid profile- TGs, TC, LDL levels, HDL levels, and liver function markers (ALP, AST, ALT) also decreased [29]. Then, kidney markers, serum urea and creatinine levels, and MDA levels also decreased, while antioxidant enzymes, including SOD, CAT, and GSH, increased [29].

Table 1: Effects of *Phyllanthus niruri* on obesity and dyslipidemia in preclinical studies

Experimental Model	Dose & Duration	Result/ Findings	Ref.
HFD-induced male Sprague-Dawley rats	8 weeks	↓ B.wt ↓TC, TG, ALT, AST, LDL, HDL, glucose, leptin, adipocyte size levels	[20]
HFD- induced male Sprague dawley rats	1000mg/kg body weight in 4 weeks	↑Adiponectin ↓Hepatic micro -macro steatosis and fibrosis ↓TNF-α, IL-6, RBP4, Vaspin, Progranulin ↓PPARγ , SLC10A2, Collagen-1α levels ↓Microvessel growth, endothelial cell migration, tube formation and VEGF secretion	[21]
MCDM induced Sprague Dawley rats	0.3, 3, 30 µg/mL 72 hours incubation in MCDM	↓ Lipid accumulation, AST, ROS, Inflammation (NF-κB) levels ↑ Lipolysis, GSH, Mitochondrial potential levels Normalized stress genes (FGF21, FXR, CHOP, CXCL5)	[22]
HFD-induced male albino rats	250 mg/kg b.wt for 105 days	↓ ALT, AST, ALP, levels ↑HDL, TP, albumin, A/G ratio levels ↓TC, TG, LDL-C, VLDL-C levels ↓Blood glucose, insulin, HOMA-IR, HOMA-β levels ↓Serum C3 Reduced micro steatosis, inflammation and necrotic hepatocyte	[23]
Aspartame (ASP) induced in female Swiss albino mice	40 mg/kg for 30 days and 60 days	↓ B.wt and O.wt ↓ ASP, TGs, ALP, AST, LDH, TGs levels ↓ROS level	[24]
(DEN) induced in male Wistar albino rats	200mg/kg for 14 weeks.	↓ B.wt, O. wt, Liver weight ↓ 8-OHdG, TBARS ↑SOD, CAT, GPx, GR and GSH levels	[25]

		↓ALT, AST, ALP, TC, TGs levels ↓GGT and LDH levels	
CCl_4 induced in male Wistar rats	1 mL/kg for 4h	↓LDH, ALP, TB, AST levels ↓TP, TC and TGs levels ↓MDA,ROS levels ↓ Oxidative stress ↓GSH, SOD ↓NF-κB, TNF-α, IL-6, IL-8, IL-10, iNOS	[26]
STZ induced male Wister rats and hypertensive rats	600 mg/kg/day for 28 days	↓TGs, SGOT, cholesterol, pancreatic islet damage levels ↑ B.wt and metabolic functions ↓ Blood glucose, MABP, ↑ Pancreas and β-cell protection	[27]
STZ-induced male Sprague Dawley rats	250 and 500 mg/kg body weight for 4 weeks	↓ Lipid profile- TGs, TC, LDL levels and increased HDL levels ↓ fasting blood glucose levels Improvement of glycolysis and gluconeogenesis, TCA cycle, ketone body synthesis and hypotaurine metabolism	[28]
STZ induced in male Wistar rats	200 and 400 mg/kg body weight for 28 days	Prevention of weight loss ↓ Lipid profile- TGs, TC, LDL levels and increased HDL levels ↓ Liver function markers- ALP, AST, ALT levels ↓ Serum urea and creatinine levels ↓ MDA level ↑ Antioxidant enzymes, including SOD, CAT, GSH	[29]

4. Role of *Phyllanthus niruri* in Diabetes

Kumar et al. showed that in streptozotocin (STZ)-induced Charles-Foster albino rats, a 250 mg/kg dose of Phyllanthus niruri for 21 days resulted in a considerable drop in blood glucose levels, suggesting a strong antihyperglycemic effect [30]. Leptin and triglyceride levels were also low after STZ treatment, although total cholesterol levels were increased [30]. Increased levels of GSH and SOD, and decreased levels of nitric oxide

(NO) and lipid peroxidation (LPO), in muscle, kidney, liver, and pancreatic tissues further demonstrated significant improvements in antioxidant defense mechanisms. These results suggest that in STZ-induced diabetes, Phyllanthus niruri exhibits antidiabetic and antioxidant-protective properties [30].

Mediani et al.'s study also found that in STZ-induced Sprague-Dawley rats, oral administration of *Phyllanthus niruri* at 250 and 500 mg/kg body weight for 4 weeks resulted in a substantial drop in blood glucose levels, indicating successful glycemic control [31]. Additionally, *Phyllanthus niruri* markedly improved the lipid profile, suggesting it may be helpful in treating dyslipidemia associated with diabetes. Overall, Mediani et al.'s study showed that *Phyllanthus niruri* had hypolipidemic and antihyperglycemic effects [31]. According to Swargiary et al., treatment with *Phyllanthus niruri* significantly increased glucose absorption in STZ-induced Wistar rats, indicating improved cellular glucose utilization [32]. This study also measured the effect of *Phyllanthus niruri* on oxidative stress and insulin sensitivity, showing decreased reactive oxygen species (ROS) levels and a significant reduction in insulin resistance [32]. Additionally, the expression of phosphorylated AMPK (pAMPK), SIRT1, PGC-1α, and GLUT4 was upregulated by *Phyllanthus niruri* treatment, and together these results imply that Phyllanthus niruri can enhance glucose homeostasis by triggering insulin signaling and energy-regulating pathways [32].

Bhushan et al. showed that streptozotocin induction can damage pancreatic β-cells, ultimately resulting in chronic hyperglycemia and related metabolic disorders [33]. *Phyllanthus niruri* treatment lowered blood glucose levels and showed antihyperglycemic action in the STZ-induced rat model. In addition to reducing glucose, it lowered dyslipidemia, indicating improved lipid metabolism and a lower risk of diabetes-related complications [33]. STZ can induce oxidative stress, which acts as a major factor in tissue damage during diabetes, and the reduction of oxidative stress can aid cells in shielding cellular structures from damage caused by free radicals. Bhushan et al. showed that treatment with *Phyllanthus niruri* reduced oxidative stress in treated animals. [33]. Raji et al. evaluated the effect of Phyllanthus niruri treatment in diabetes in a dose-dependent manner [34]. *Phyllanthus niruri* treatment at graded levels (50, 75, and 125 mg/kg) improved glucose metabolism in Wistar rats in a dose-dependent manner. Inhibition of α-amylase and α-glucosidase can slow intestinal carbohydrate breakdown and delay glucose absorption; this study showed that, after *Phyllanthus niruri* treatment, postprandial hyperglycemia was controlled [34]. Oxidative stress was also significantly reduced, suggesting defense against STZ-induced free-radical damage. *Phyllanthus niruri* treatment showed increased hexokinase activity at the enzymatic level, indicating improved peripheral tissues' ability to use glucose [34]. Glycogen levels were also higher, indicating enhanced insulin sensitivity and glucose storage. IR, Akt, GLUT4, and Nrf2 gene expression were all elevated at the molecular level by the therapy, indicating that the insulin signaling pathway and antioxidant defense mechanisms were activated. Taken as a whole, these molecular alterations enhance insulin responsiveness, glucose uptake, and cellular resistance to metabolic stress [34].

Table 2: Effects of *Phyllanthus niruri* on Diabetes in preclinical studies

Experimental Model	Dose & Duration	Result/ Findings	Ref.
STZ-induced Charles-Foster (CF) albino rats	250 mg/kg for 21 days	↓ blood glucose level ↓Triglycerides and Leptin level ↑ Cholesterol level ↑ GSH & SOD while ↓ NO, LPO in Muscle, kidney, Liver and Pancreas tissues.	[30]
STZ-induced Sprague–Dawley rats	- 250, 500 mg/kg for 4 weeks	↓ Serum Glucose level ↑ Lipid profile level	[31]
STZ-induced Wistar rats		↑ Glucose uptake level ↓ ROS level ↓ Insulin resistance ↑ SIRT1, PGC-1α, pAMPK, GLUT4 gene expression	[32]
STZ-induced albino mice		↓ Blood glucose level ↓ Dislipidemia level ↓ Oxidative stress DPP-IV inhibition	[33]
STZ-induced Wistar rats	- 50, 75, 125 mg/kg	α-amylase, α-glucosidase inhibition ↓ Oxidative stress ↑ Hexokinase activity ↑ Glycogen level ↑ IR, Akt, GLUT4, Nrf2 gene expression	[34]

5. Role of *Phyllanthus niruri* in Chronic Kidney Disease

Reduced glomerular filtration rate or indicators of kidney damage, such as albuminuria, electrolyte imbalance, or structural and histological abnormalities, are used to diagnose chronic kidney disease (CKD), a long-term condition characterized by persistent abnormalities in kidney structure or function lasting longer than three months [35]. With an overall prevalence of 10–14% among adults, CKD is a significant and expanding global public health concern that affects about 800 million people worldwide. It is currently one of the top ten causes of death worldwide and is primarily caused by the rising burden of diabetes, hypertension, and an aging

population [36]. South Asian nations, especially Bangladesh, have a disproportionately greater burden of CKD, with prevalence ranging from 13% to 26% and a pooled prevalence of around 22.5%, which is higher than the world norm [37]. Both non-modifiable risk variables, such as advanced age, genetic predisposition, sex, and family history of kidney disease, affect the onset and course of CKD [38], as do variables such as diabetes, high blood pressure, obesity, smoking, physical inactivity, abuse of nephrotoxic medications like NSAIDs, and use of some antibiotics; low socioeconomic status, low health awareness, and limited access to healthcare services, especially in low- and middle-income nations, increase the chances of CKD [39].

The kidneys primarily remove oxalate, a hazardous metabolic byproduct, via tubular secretion and glomerular filtration. Oxalate builds up in the renal tubules in conditions such as primary or enteric hyperoxaluria or due to excessive consumption of oxalate or its precursors (such as ethylene glycol) [40]. Increased tubular oxalate encourages the production of calcium oxalate crystals, which cause tubular blockage, damage to epithelial cells, and gradual renal impairment, all of which can result in a significant drop in glomerular filtration rate (GFR) [40]. Long-term high NaCl consumption leads to salt and volume retention, thereby increasing intraglomerular pressure and sustaining hypertension. This leads to elevated oxidative stress, decreased nitric oxide, and endothelial dysfunction. Glomerulosclerosis and tubulointerstitial fibrosis are caused by persistent inflammation and activation of fibrotic pathways, including TGF-β signaling. CKD results from progressive nephron loss [41]. Nicotinamide (NA) and streptozotocin (STZ) are utilized as diabetogenic drugs that induce diabetes and diabetic kidney disease (nephropathy) in animal models. Complications from diabetic nephropathy might result from persistent hyperglycemia. High blood sugar (caused by STZ) activates Protein Kinase C (PKC) and increases Angiotensin II activity in the kidneys [41]. Angiotensin II constricts blood vessels, raising pressure inside the kidney's filtering units (glomeruli), and PKC triggers inflammation, oxidative stress, and scarring (fibrosis) in the kidney tissue. Combined tissue damage from PKC and Angiotensin II destroys the filters, leading to a progressive decline in eGFR (estimated Glomerular Filtration Rate), signaling kidney failure [41].

Renal tubule hypertrophy is triggered by insulin-like growth factor-1 (IGF-1), VEGF, and endothelin-1 (ET-1). Tumor necrosis factor-α (TNF-α), nuclear factor kappa B (NFκB), and fibrotic factors, including connective tissue growth factor (CTGF) and transforming growth factor-ß (TGF-β), can all be stimulated by protein kinase C [42]. Both fibrotic factors lead to glomerular hypertrophy, mesangial enlargement, and increased connective tissue proliferation. PKC also increases the production of inflammatory cytokines that can lead to glomerulosclerosis, thereby worsening the decline in antioxidant enzyme activity [42]. Chronic oxidative and tubular damage is the primary cause of paracetamol-induced CKD [43]. Overuse or prolonged use of paracetamol increases the production of the hazardous metabolite NAPQI, which promotes oxidative stress in renal tubular cells and depletes glutathione levels, leading to interstitial fibrosis, inflammation, and proximal tubular necrosis. CKD is the result of a gradual loss of nephron function and decreased GFR caused by repeated damage [43]. D-galactosamine (GalN) causes renal damage mostly by oxidative stress, which increases lipid peroxidation and depletes antioxidant defenses, including GSH, SOD, and CAT. Compromised antioxidant defense leads to tubular

cell damage and dysfunction [44]. In the context of acute hepatic damage or hepatorenal physiology, it also induces inflammatory activation and subsequent hemodynamic alterations (e.g., renal vasoconstriction, decreased GFR). These mechanisms lead to CKD symptoms and a gradual decline in renal function [44]. Administering alloxan induces long-term hyperglycemia and oxidative stress, producing ROS that harm renal cells, promote inflammation, and increase profibrotic factors such as TGF-β1 [45]. In experimental models, this results in glomerulosclerosis, tubular damage, and interstitial fibrosis, which are characteristics of CKD progression. Increased extracellular matrix buildup and apoptosis are other consequences of elevated p53 and TIMP-1, which directly contribute to kidney damage, reduced filtration, increased serum creatinine and blood urea nitrogen (BUN), and structural renal decline [45].

Persistent renal damage and maladaptive repair are the main causes of CKD, which results in gradual nephron loss and functional deterioration. Glomerulosclerosis and tubulointerstitial fibrosis are the molecular outcomes of CKD development, which entails persistent activation of fibrotic, inflammatory, oxidative, and metabolic stress pathways[46]. At the molecular level, fibrosis, inflammation, and oxidative stress propel the development of chronic kidney disease [38]. Pro-fibrotic cytokines, particularly transforming growth factor-β (TGF-β1), promote the deposition of extracellular matrix, which leads to tubulointerstitial fibrosis and glomerulosclerosis [47]. Kidney injury and systemic consequences are further accelerated by endothelial dysfunction and uremic toxin buildup [48]. Chronic hyperglycemia causes oxidative stress, podocyte damage, and mitochondrial dysfunction in metabolic diseases like diabetes, which leads to diabetic kidney disease, the world's most common cause of chronic kidney disease [49].

Phyllanthus niruri is chosen for the treatment of chronic kidney disease (CKD) because of its potent renoprotective properties, including anti-inflammatory, antifibrotic, and antioxidant activities. By reducing oxidative stress and inflammatory pathways, it can enhance renal function and lessen toxin-induced kidney damage.

In a Ca-oxalate-induced male C57BL/6 mouse model, once-daily administration of 80 mg/kg Phyllanthus niruri for 7 days significantly reduced kidney damage, as reported by Mao Ting Li et al. [50]. The results show improved renal function, as indicated by decreased blood creatinine and kidney calcium content. During *Phyllanthus niruri* treatment, MDA levels were reduced, and GPx activity was elevated, which attenuated oxidative stress, implying that antioxidant defenses provided by *Phyllanthus niruri* can prevent calcium oxalate (Ca-Ox) crystal-induced damage [50].

At the molecular level, the therapy reduced cellular stress and death by suppressing p53 expression and downregulating genes involved in lipid metabolism (SQLE, HMGCS1, and SCD). Histopathological results showed further protection, with reductions in inflammation, crystal deposition, and tubulointerstitial damage following *Phyllanthus niruri* treatment [50]. Khairil Fahmi et al.'s study evaluated *Phyllanthus niruri* for Salt-Induced Kidney Damage [51]. High salt intake causes the kidneys to permanently remodel their structure, leading to scarring. In the 2% NaCl-induced female Wistar rat model, *Phyllanthus niruri* treatment dramatically reduced

extracellular matrix (ECM) accumulation and fibrosis over 4 weeks, indicating its ability to prevent salt-induced renal structural damage and the progression of CKD. [51]. According to Giribabu et al., administering *Phyllanthus niruri* at doses of 200 and 400 mg/kg body weight for 28 days effectively improves renal and metabolic dysfunction in a male Wistar rat model of STZ–NA-induced diabetes [52]. Serum creatinine, urine creatinine, urine output, serum urea, BUN, serum uric acid, urine protein, and serum Na+ and K+ levels all decreased in a dose-dependent manner with Phyllanthus niruri therapy, indicating its ability to improve kidney function. Creatinine clearance (Ccr) activity, on the other hand, is markedly elevated, indicating improved glomerular filtration [52]. Antioxidant enzyme activities (SOD, CAT, and GPx) are significantly lower in the oxidative stress indicators than in the diabetes control group. Furthermore, the medication significantly reduces the expression of inflammatory mediators, including NF-κB, IκBβ, TNF-α, and interleukins (IL-1β and IL-6). Histopathological examination reveals reduced renal fibrosis and apoptosis, supporting the treatment's renoprotective effects [52]. Freitas et al. report that in CaOx seed-induced adult male Wistar rats, oral treatment with *Phyllanthus niruri* at 1.25 mg/mL/day for 42 days dramatically reduces nephrolithiasis-associated biochemical changes [53]. The medication lowers creatinine levels and urine Na^+, K^+, uric acid, and oxalate levels; however, urine Ca^{2+} levels remain stable. Plasma biochemical examination showed decreases in Na^+, potassium oxalate, K^+, Mg^{2+}, Ca^{2+}, and uric acid levels [53]. In addition, the therapy dramatically reduces renal calculus weight and glycosaminoglycan (GAG) content, indicating suppression of stone formation and crystal aggregation compared with CaOx-induced control mice [53].

The study by Da'i et al. reports that Phyllanthus niruri exhibits antioxidant properties that protect rats against paracetamol-induced oxidative damage [54]. During their experiment, they noted that in a paracetamol-induced rat model, oral administration of paracetamol at dosages of 50, 100, and 200 mg/kg body weight for 8 days caused oxidative stress-related damage; on the other hand, *Phyllanthus niruri* treatment reduced malondialdehyde (MDA) levels in a dose-dependent manner, indicating its potential to reduce lipid peroxidation and oxidative damage [54]. Shanmugam et al. studied Phyllanthus niruri's hepatoprotective property. They administered *Phyllanthus niruri* at doses of 100 and 800 mg/kg body weight to male Wistar rats for 21 days, in a dose-dependent manner [55]. The treatment improved metabolic parameters and enhanced hepatic and renal function, as evidenced by decreased serum bilirubin and creatinine levels. Additionally, there was a significant decrease in the activity of the liver enzymes AST and ALT, suggesting hepatoprotective effects and stability of the hepatocellular membrane [55]. Yuniarti et al. also support *Phyllanthus niruri's* hepato-renal protection potential [56]. They reported that in a male Wistar rat model treated with *Phyllanthus niruri* extract, oral administration at doses of 1.35, 2.7, and 5.4 mg/kg body weight for 4 weeks resulted in substantial biochemical improvements [56]. There was a dose-dependent reduction in blood glucose level, serum creatinine, and blood urea nitrogen (BUN) levels, indicating nephroprotective action. Furthermore, the extract significantly reduced AST and ALT activities, indicating that it protects liver function and confirms *Phyllanthus niruri*'s hepato-renal protective potential [56].

Table 3: Renoprotective effects of *Phyllanthus niruri* in preclinical studies

Experimental Model	Dose & Duration	Result/ Findings	Ref.
Ca-ox induced Male C57BL/6 mice	80 mg/kg once daily for 7 days	↓ Kidney calcium content, Serum creatinine level ↓MDA level with ↑ GPx activity, Ca-Ox deposition level ↓ SQLE, HMGCS1, SCD gene expression ↓ p53 expression ↓ Tubulointerstitial injury, crystal deposition and inflammation	[50]
NaCl induced female Wistar rat	2% NaCl in drinking water for 4 weeks	↑ ECM ↓ Fibrosis	[51]
STZ-NA induced male diabetic Wistar rats	- 200, 400 mg/kg for 28 days	↓ serum creatinine, urine creatinine, urine output (mL), serum urea, BUN, serum uric acid, urine protein, Na^+, k^+ level in a dose dependent manner ↑ Ccr activity ↓ SOD, CAT and GPx activity ↑NF-kβ, Ikkβ, TNF-α and ILs (IL-1β and IL-6) gene expression ↓ Fibrosis and apoptosis	[52]
CaOx seed induced adult male Wistar rats	administered orally at 1.25 mg/mL/day for 42 days.	↑ creatinine level ↑ Na^+, K^+, ↓ uric acid, Oxalate and no change in Ca^{2+} in Urinary analysis ↓ Na^+, Oxalate, ↑ K^+, Mg^{2+}, Ca^{2+}, Uric Acid in Plasma analysis ↓ Calculus weight ↑ GAG content	[53]
Paracetamol induced Rat	- 50,100,200 mg/kg for 8 days	↓ MDA level in a dose dependent manner	[54]
D-Galactosamine-induced male Wistar rat	- 100, 800 mg/kg for 21 days	↓ Bilirubin, creatinine level in a dose dependent manner ↓ AST, ALT activities level in a dose dependent manner	[55]

Alloxan-induced male wister rats	- 1.35, 2.7, 5.4 mg/kg for 4 weeks	↓ Blood glucose level in dose dependent manner ↓ Creatinine and BUN level in a dose dependent manner ↓ AST, ALT activities level in a dose dependent manner	[56]

6. Role of *Phyllanthus niruri* in Hepatic fibrosis

The liver, the largest parenchymal organ in the human body, is responsible for many functions, including protein synthesis, metabolism, immune response, endocrine regulation, biotransformation of nutrients, and detoxification [57]. As a result, disorders in liver function can be caused by numerous hepatic illnesses, such as viral hepatitis, fatty liver, hepatic fibrosis, hepatic cirrhosis, and hepatocellular carcinoma (HCC), which pose a serious threat to human health and cause more than 2 million deaths worldwide each year [57]. In a chronic condition, fibrous tissue replaces liver parenchyma, separating functional hepatocytes into isolated nodules. Severe disruption of tissue structure can cause liver failure, including loss of metabolic and synthetic function, portal hypertension, ascites formation, and portal-systemic shunting [58]. Also, one of the most dangerous aspects of liver illness and a potentially catastrophic consequence of hepatic failure is uncontrolled bleeding due to insufficient synthesis of blood-clotting factors [58]. In addition, it is the sole organ capable of regenerating itself. Hepatoxins, such as numerous environmental pollutants, poor diet, excessive alcohol consumption, and drug overdoses, interact with cellular macromolecules to cause liver damage [59].

Hepatitis is characterized by liver inflammation and edema. The term is frequently used to describe a hepatic viral infection but there are other causes as well, such as viral infections (like Hepatitis A, B, C, D, and E), autoimmune response, infections from bacteria or parasites, heavy alcohol use or poisonous mushrooms, fatal overdoses of acetaminophen or inherited disorders like cystic fibrosis or hemochromatosis, and Wilson's disease [60]. Abdominal pain or distention, dark urine, pale or clay-colored feces, exhaustion, typically low-grade fever, generalized itching, jaundice (yellowing of the skin and eyes), loss of appetite, nausea, vomiting, and weight loss are some of the symptoms of hepatitis. [60]. In both Europe and the US, one of the most common liver illnesses is alcoholic liver disease (ALD). The largest risk of ALD4 is associated with chronic, excessive alcohol use. Consuming >40 g of pure alcohol daily (equivalent to 375 ml of 13 vol% wine or >1 liter of 5 vol% beer) for an extended period of time (years) can cause ALD [61]. According to a recent meta-analysis, compared to non-drinking individuals, even chronic alcohol consumption of 12–24 g daily can increase the chance of cirrhosis, a late stage of ALD. Alcoholic fatty liver (AFL), which is defined by hepatic steatosis (a buildup of triglycerides in hepatocytes), is the first stage in the spectrum of ALD [61]. Alcoholic steatohepatitis (ASH) is characterized histologically by hepatic inflammation, hepatocyte damage, and ballooning in certain individuals. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver

(EASL) have published clinical guidelines for the management of alcohol use disorder (AUD), as well as nutritional, pharmaceutical, and surgical interventions for decompensated (symptomatic) liver disease [61].

Globally, nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. It is frequently linked to metabolic risk factors such as obesity, dyslipidemia, hypertension, and diabetes, and is thought to be the hepatic manifestation of metabolic syndrome [62]. In people with at least 5% of hepatocytes infiltrated with steatosis or a magnetic resonance imaging proton density fat fraction [MRI-PDFF] of 5% or higher, or a magnetic resonance spectroscopy liver fat content of more than 5.56% in people who drink little or no alcohol and have no secondary causes of hepatic steatosis, such as other metabolic liver diseases (such as Wilson's disease, congenital or acquired lipodystrophy) or drugs (e.g., amiodarone, steroids, valproic acid, etc.), NAFLD is diagnosed using either an imaging or a liver biopsy [62]. NAFLD (now also called MASLD) is diagnosed using imaging or liver biopsy after ruling out significant alcohol use and other secondary causes of liver fat (such as specific medications or rare metabolic diseases). It is confirmed when patients have at least one of the following: at least 5% of hepatocytes infiltrated with steatosis, or a magnetic resonance imaging proton density fat fraction [MRI-PDFF] of 5% or higher, or Magnetic resonance spectroscopy (MRS) liver fat content above 5.56% [62]. Nonalcoholic fatty liver (NAFL), the non-progressive form of NAFLD, and NASH, the progressive form of NAFLD, are the two major subtypes of NAFLD. The presence of steatosis, lobular inflammation, and ballooning, with or without perisinusoidal fibrosis, is a common feature of NASH and necessitates histological evaluation in the setting of suspected NAFLD. Liver damage that progresses to cirrhosis and HCC (Hepatocellular Carcinoma) may occur in a subset of people with NASH [62]. The term "liver cirrhosis" refers to fibrosis and scarring of liver tissue caused by chronic liver disease, characterized by regenerating nodules encircled by fibrous bands. For people with chronic liver disease, cirrhosis is a major cause of morbidity and death. Cirrhosis was thought to be responsible for 2.4% of fatalities worldwide in 2019 [63]. In 2017, there were an estimated 112 million instances of compensated cirrhosis and roughly 10.6 million cases of decompensated cirrhosis worldwide. Other factors responsible for chronic liver disease are alcohol use disorder, HCV, and non-alcoholic fatty liver disease (NAFLD; also known as metabolic dysfunction-associated steatosis liver disease, or MASLD), which account for 45%, 41%, and 26% of instances of liver cirrhosis, respectively [63]. The paradigm has more recently evolved toward NAFLD and alcohol use as the primary causes of cirrhosis, with NAFLD accounting for 61.8% of incident cases and alcohol use disorder accounting for 20.0% of cases due to treatment breakthroughs and the potential for a cure of HCV infection [63]. It has been demonstrated that people with liver cirrhosis respond better to evidence-based treatments that address the disease's etiology and consequences. Although liver transplantation is presently the only treatment available for cirrhosis, recent developments in pharmacological therapy offer the potential to both stop and reverse the disease's progression [63]. AIH is a rare, progressive, chronic inflammatory liver disease that affects people of various ages and races, and the underlying cause is unknown. Type 1 and Type 2 are the two main subtypes of AIH. People of all ages can be affected by type 1 AIH, with peak incidence in adolescence and a second rise in adults around age 40 [63].

Serological evidence of anti-nuclear antibody (ANA), with or without anti-smooth muscle antibody (SMA), is linked to it. Conversely, children and adolescents are primarily affected by Type 2 AIH. Anti-liver kidney microsomal type 1 (anti-LKM1) antibody, with or without anti-liver cytosol type 1 (anti-LC1) antibody, is associated with 75% of AIH cases, regardless of subtype [64]. T-helper cell-mediated recognition of liver autoantigens and B-cell generation of autoantibodies initiate the self-attack of AIH, which is sustained by a decrease in the quantity and activity of regulatory T-cells. In addition to a genetic predisposition, environmental factors and infections have been investigated as triggers for various disorders [64].

Ezzat et al. conducted standard liver function tests (LFTs): ALT, ALP, TB, and AST in the CCl_4-induced male Wistar rat model with *Phyllanthus niruri* [26]. In a dose-dependent manner, *Phyllanthus niruri* treatment at 25, 50, 100, and 200 mg/kg body weight decreases ALT, ALP, TB, and AST levels, and reduces TC, TG, Urea, and creatinine levels, but does not change glucose levels [26].

The inflammatory markers, such as NF-KB, IL-6, IL-8, IL-10, and TNF, decreased, respectively, and, compared to the CCL_4 rats, *Phyllanthus niruri* treatment neutralized the effects of the antioxidant enzymes SOD, CAT, GSP, and GR by increasing their levels [26]. The histopathological study showed a reduction in ballooning degeneration, fatty changes, necrosis, and inflammatory cell infiltration, with marked congestion [26]. Kodoli et al. reported that doses of 50 and 100mg/kg of *Phyllanthus niruri* for 5 days, respectively, reduce the levels of SGPT, SGOT, SLAP, total bilirubin, direct bilirubin, total cholesterol, and proteins, and increase the levels of CAT and SOD [65]. The histopathology study shows that both treated groups (50 and 100mg/kg *Phyllanthus niruri*) reduce hepatic tissue damage, with no focal hemorrhage and only slight ballooning of hepatocytes on H&E staining [65]. Hashem et al. state that the extract of 250mg/kg doses *Phyllanthus niruri* decreased the rate of liver enzyme markers (ALT, AST, ALP) in the selected rats, significantly reduced the level of total cholesterol (TC), Triglycerides (TG), VLDL, LDL, and HDL when applied for 105 days on a high-fat diet (HFD) induced male albino rats [66]. Although *Phyllanthus niruri* reduced the levels of the diabetes markers (glucose, insulin, and HOMA-IR), no change in serum bilirubin or HOMA-β level was observed. It also increased albumin levels, the A/G ratio, total protein (TP), globulin, and C3 [66]. Dey et al. also reported on the hepatoprotective activity of *Phyllanthus niruri* [67]**.** Treatment with *Phyllanthus niruri* in CCl_4, along with 40% alcohol, in male and female Sprague- Dawley rats showed a decrease in liver enzyme biomarkers, and some selected rats showed an improvement in total body weight. In this study, *Phyllanthus niruri* was combined with *Tephrosia purpurea, Boerhavia diffusa,* and *Andrographis paniculata,* at doses of 250 and 500 mg/kg for 21 days [67]. The study by Khanth et al. found that 125mg/kg *Phyllanthus niruri*, in combination with *A. paniculata*, administered for 14 days to isoniazid-rifampicin-induced Sprague Dawley rats, decreased the levels of total bilirubin, SGOT, SOD, and catalase [68]. There was no evidence of necrosis during staining, unlike in the disease-induced group [68]. Simarmata et al. found that a combination of Snakehead Fish Extract (Channa striata), Meniran (Phyllanthus niruri L.), and Temulawak (Curcuma xanthorrhiza) improved liver function in HFD-induced diabetes in male Rattus norvegicus rats [69]. Histopathology revealed administration of combined capsule improved liver structure

and decreased fat accumulation [69]. Khandia et al. reported that *Phyllanthus niruri* (200µl) significantly decreases the levels of liver enzyme markers (AST, ALT, ALP); kidney functional biomarkers (creatinine, BUN); amylase; and lipid biomarkers (cholesterol, triglyceride, protein, albumin) when applied to Imidacloprid-induced chicken embryos for 17 days [70]. Besides, Hematoxylin and eosin (H&E) staining in the histological investigations revealed that in sections of the chicken embryo liver, there were signs of reduced necrosis, normal sinusoids, dilated blood sinusoids (DBS), bile ducts (BD), and CVR (central vein with RBCs) [70].

Naik et al. showed that aspartame-induced female Swiss albino mice, Mus musculus, received 100 mg/kg of *Phyllanthus niruri* for 30 and 60 days, respectively, and that following treatment was available to reduce liver enzyme markers (ALT, ALP, AST, GGT, LDH), bilirubin, and hepatic total protein, relative hepatic weight; renal enzyme markers (ALP, AST, ALT, and creatinine); relative renal weight; glucose, cholesterol, and triglycerides [71]. Additionally, their histopathological investigations showed that lobular structure returned to normal, the polyhedral arrangement of hepatocytes around the central vein was normal, hepatic cells enclosed the hepatic sinusoids, and inflammation was reduced [71,72]. Al Zarzour et al. reported that a 1000 mg/kg dose of *Phyllanthus niruri* administered for eight weeks to male Sprague Dawley rats fed a high-fat diet significantly decreased the levels of AST, ALT, ALP, and AST/ALT, obesity-related metabolic dysfunction, insulin resistance biomarkers (Adiponectin, RBP4, Progranulin, and Vaspin), as well as the weight of the liver and visceral fat [73]. Serum TNFα, IL-6, PPARγ, SLC10A2, CFD, PNPLA2, and COL1α1 levels were lower than those of the only high-fat diet group. Hematoxylin and eosin (H&E) staining in the histological investigations revealed no evidence of fibrosis, steatosis, or inflammation. The hepatoprotective properties of *Phyllanthus Niruri* are confirmed by the entire investigation [73]. According to Balakrishnan et al., 200 mg/kg of *Phyllanthus niruri* for two weeks decreased serum enzyme markers (AST, ALT, ALP), reduced the hepatic lipid profile, increased serum protein, and increased hepatic TBARS concentration, and inhibited hepatic lipid peroxidation in CCl4- and coconut oil-induced female Swiss albino mice [74]. These findings suggest that *Phyllanthus niruri* may have hepatoprotective effects. Hematoxylin and eosin staining was used for histomorphological investigation, which revealed no fatty arrangement of hepatic cells and no necrosis; the cells had distinct cytoplasm, nuclei, and prominent central veins [74]. Shanmugam et al. used 800 mg/kg body weight of *Phyllanthus niruri* to treat male Wistar rats that had been intraperitoneally given D-galactosamine [75]. AST, ALT, bilirubin, and creatinine levels all dropped after *Phyllanthus niruri* treatment. Conversely, the urea level was considerably higher. The histological investigations revealed signs of regeneration of the sinusoids, hepatocytes, and central veins [75].

According to Manonmani et al., 100 mg/kg of *Phyllanthus niruri* for 20 days reduced blood levels of liver enzymes (AST, ALT, and ALP) in male Swiss albino mice treated with CCl_4 in diluted olive oil, suggesting it can protect liver function [76]. Additionally, it lowers glucose, albumin, globulin, total protein, and cholesterol. However, the Total White Blood Cell Count (TWBC) decreased, while the hematological parameters (RBC, PCV, HB, and platelets) increased [76]. Hematoxylin and Eosin staining was used for the histopathology investigations, which revealed decreased necrosis, fewer inflammatory cells, and hepatic cell regeneration [76]. Novianta et al.

found that when Wistar rats were given 200 mg/kg b.w. of *Phyllanthus niruri* for 7 days after paracetamol treatment, AST, ALP, ALT, and bilirubin levels decreased, while total protein (TP), GSH, LPO, and catalase levels increased [77]. Additionally, the histological analysis revealed reduced hepatic membrane damage, inflammatory cell infiltration, and necrosis. [77]. Ramamurthy et al. showed that administering 300 mg/kg of *Phyllanthus niruri* to aflatoxin-induced Wistar albino rats for 40 days decreased serum levels of liver enzymes (SGOT, SGPT, ALP, & bilirubin) while increasing total protein, platelets, WBC, and neutrophils [78]. The therapeutic effects of the plant extract were confirmed, as it reversed aflatoxin-induced anemia and immunosuppression by restoring depleted levels of RBC, Hb, PCV, and lymphocytes toward normal ranges [78].

Table 4: Hepatoprotective effects of *Phyllanthus niruri* in preclinical studies

Experimental model	Dose & Duration	Result/Findings	Ref.
CCl_4-induced male Wistar rats	25,50,100, and 200 mg/kg	↓ ALT, ALP, TB, and AST levels in a dose-dependent manner. ↓ TC, TG. No change in Glucose level. ↓urea, and creatinine. ↑ GSH, ↓ ROS, MDA. ↓ NF-kB, IL-6, IL-8, IL-10, TNF ↑ SOD, CAT, GSP, and GR. ↓ Ballooning degeneration, fatty changes, necrosis, and infiltration of inflammatory cells infiltration, and marked congestion in a dose-dependent manner.	[26]
CCl_4-induced albino Wistar rats	50mg/kg,100mg/kg, and 50 and 100mg/kg for 5 days.	↓ SGPT, SGOT, SALP, total bilirubin, direct bilirubin, ↓ TC, total proteins, and LPO. ↑ CAT and SOD. ↑ Repair of hepatic tissue damage	[65]
HFD-induced male albino rats	250mg/kg for 105 days	↓ ALT, AST, ALP ↓ TC, TG, VLDL-c, LDL-C, ↑ HDL-c ↓ glucose, insulin, and HOMA-IR. no change in serum bilirubin, HOMA-β level. ↑ Albumin & A/G ratio, TP, Globulin. C3 levels	[66]
CCL_4, along with 40% alcohol,	*Phyllanthus niruri* combined with *Tephrosia purpurea,*	↓ ALT, ALP, Serum bilirubin, AST TP remained similar ↑ B.W. loss	[67]

induced male and female Sprague-Dawley rats	*Boerhavia diffusa,* and *Andrographis paniculata* 250 and 500 mg/kg b.w. for 21 days		
Isoniazid and Rifampicin induced Sprague Dawley rats	*P.niruri* combined with *A. paniculata* 125mg/kg, PO for 14 days.	↓Total bilirubin, SGOT. ↓ SOD, Catalase enzymes. No signs of necrosis.	[68]
HFD-induced diabetic mellitus male *Rattus norvegicus* rats	capsule combination of *Channa striata, P.niruri,* and *Curcuma xantorrhiza*	Improved liver functions	[69]
Imidacloprid-induced chicken embryos	200µl extract of *P. niruri* for 17 days	↓ AST, ALT, ALP. ↓ Creatinine, BUN. ↓ Amylase. ↓Cholesterol, TG, Protein, Albumin. ↓Necrosis, DBS, BD, CVR.	[70]
CCl_4-induced male albino rats	*P. niruri* combined with *Plantago major* (500 mg/kg/day) for 31 days.	↓ TNF-α, IL-1β, and IL18 ↓ MDA with ↑ SOD, GSH level	[71]
Artificial sweeteners, aspartame-induced female Swiss albino *Mus musculus*	100mg/kg for 30 and 60 days	↓ ALP, ALT, AST, GGT, LDH, bilirubin, hepatic TP. ↓ renal ALP, renal AST, renal ALT, renal creatinine. ↓ glucose, cholesterol, triglyceride. ↓ nercosis, inflammatory cells.	[72]
HFD-induced male Sprague-Dawley rats	1000 mg/kg for 8 weeks	improved liver histology, ↓ adiponectin, RBP4, TNFα, IL-6, progranulin,and vaspin. no signs of inflammation, steatosis, or fibrosis. ↓ PPARγ, SLC10A2, and Collα1.	[73]

CCl_4 with coconut oil induced female Swiss albino mice	200mg/kg for 2 weeks	↓ AST, ALT, ALP, hepatic lipid profile. ↑ Serum total protein, lipid peroxidation. ↓ Necrosis, inflammatory cells.	[74]
D-Galn induced male Wistar rats	800mg/kg for 21 days	↓ AST, ALT, bilirubin. ↓ creatinine,↑urea. ↓ necrosis, inflammation cells.	[75]
CCl_4 with diluted olive oil induced male Swiss albino mice	100mg/kg for 20 days	↓ AST, ALT, ALP, bilirubin, liver weight. ↓ TP, Albumin, Globulin, cholesterol. ↓ glucose ↑ RBC,P CV, HB, Platelet.↓ TWBC. ↓ fatty change, necrosis, and lymphocyte infiltration.	[76]
Paracetamol induced Wistar rats	200mg/kg for 7 days	↓ AST, ALP, ALT, bilirubin. ↑ TP ↑ GSH, LPO, Catalase. ↓ necrosis, inflammatory cells.	[77]
Aflatoxin-induced Wistar albino rats	300mg/kg *P. niruri* for 40 days	↓ SGOT, SGPT, ALP, bilirubin. ↑ Protein. ↓ RBC, Hb, PVC, MCV, MCH, MCHC, lymphocyte, ↑platelet, WBC, neutrophils.	[78]

7. Role of *P. niruri* on Inflammation

The immune system's basic biological reaction to damaging stimuli, including infection, tissue damage, poisons, or autoimmune responses, is inflammation. Its main goals are to remove damaged tissue, initiate the healing process, and eliminate the original cause of cell damage [79]. Blood vessels, immune cells, and chemical mediators such as chemokines and cytokines work together to cause inflammation. Even though inflammation has a protective function, imbalance of this process can lead to the onset of illness [79]. According to epidemiological statistics, indicators such as high-sensitivity C-reactive protein (hs-CRP) indicate that a significant proportion of people have increased systemic inflammation. A total of 12,946 unweighted individuals, or 315,354,183 adults in the United States, were evaluated. 34.63% of people suffer from systemic inflammation [80]. 15.1%, 29.1%, and 41.8% of those 20 years of age and older had no disease, undiagnosed disease, and diagnosed disease with inflammation, respectively. Non-Hispanic Black persons had the highest prevalence

(50.35%) among those with a diagnosis of increased inflammation when stratified by race/ethnicity, followed by Hispanics (46.13%) and Non-Hispanic Whites (40.15%) [80]. Causes of inflammation can be both external and internal, according to original epidemiological research, the main causes of high systemic inflammatory markers are age, obesity, smoking, poor food, and sedentary lifestyle. Chronic low-grade inflammation is facilitated by the active secretion of pro-inflammatory cytokines including TNF-α and IL-6 by adipose tissue, particularly visceral fat [81].The acute inflammatory model of carrageenan-induced inflammation is typified by a biphasic reaction. The release of bradykinin, serotonin, and histamine mediates the early phase (0–2 h), leading to increased vascular permeability and edema development [82].

Prostaglandins, nitric oxide, and pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) via COX-2 and NF-κB activation are the key drivers of the late phase (3–6 h). Oxidative stress and neutrophil infiltration worsen tissue damage and prolong inflammation [82]. By attaching itself to Toll-like receptor-4 (TLR4) on immune cells including macrophages and monocytes, lipopolysaccharide (LPS) causes inflammation. Pro-inflammatory mediators (TNF-α, IL-1β, IL-6, COX-2, and iNOS) are released after downstream MyD88- and TRIF-dependent signaling pathways are activated, causing NF-κB and IRFs to translocate into the nucleus. Endothelial dysfunction, tissue damage, and systemic inflammatory reactions are brought on by an overabundance of cytokines and reactive oxygen/nitrogen species [83]. When LPS binds to TLR4 on macrophages, the MyD88/NF-κB signaling cascade is activated, increasing the production of pro-inflammatory mediators such as CCL2, IL-1β, TNF-α, and IL-6 and encouraging inflammatory responses and death in alveolar macrophages [84]. In acute lung injury, the TLR4/MyD88/NF-κB axis stimulates the production of cytokines and chemokines that increase the recruitment of inflammatory cells and tissue damage. Circ-Phkb downregulation attenuates inflammation in LPS-induced macrophages via lowering CCL2 production and NF-κB activation [84].

According to Sutrisna et al., the administration of *Phyllanthus niruri* at doses of 250, 500, and 1000 mg/kg body weight significantly reduced paw edema volume in a dose-dependent manner in a carrageenan-induced Swiss albino rat model, suggesting a strong anti-inflammatory effect compared with the carrageenan control group [85]. The anti-inflammatory potential of the natural compound was further confirmed in another experiment by Ronia Mostofa et al., using a carrageenan-induced model in female Swiss albino rats. Treatment at doses of 100, 200, and 400 mg/kg body weight resulted in a significant, dose-dependent decrease in edema volume [86]. In Swiss Webster rats induced with 1 mL of 1% acetic acid, Dian Arsanti Palupi et al. showed that a combination of dry extracts of *Phyllanthus niruri* (Meniran) and *Moringa oleifera* leaves exhibited significant analgesic activity, as evidenced by a decreased pain response compared to the control group [87]. Hossain et al. demonstrated that administering the extract at a concentration of 400 mg/kg for 4 hours significantly decreased edema volume in male and female Swiss albino rats produced with carrageenan, indicating an efficient acute anti-inflammatory response in both genders [88]. According to Jeje et al., treatment with 20 mg/kg of *Phyllanthus niruri* for two days significantly reduced IFN-γ concentrations in blood serum, decreased albumin denaturation,

and suppressed enzyme release in an LPS-induced inflammatory model using female C57BL/6 mice, indicating potent anti-inflammatory and immunomodulatory effects compared to the LPS-treated control group [89].

Table-5 Effects of *Phyllanthus niruri* on inflammation in preclinical studies

Experimental Model	Dose & Duration	Result/ Findings	Ref.
Carrageenan-induced Swiss albino rats	- 250, 500, 1000 mg/kg	↓ Edema volume in a dose dependent manner	[85]
Carrageenan-induced female Swiss albino rats	- 100, 200, 400 mg/kg	↓ Edema volume in a dose dependent manner	[86]
Combination of dry extracts of meniran leaves (*Phyllanthus niruri*) and moringa leaves (*Moringa oleifera*) induced Swiss Webster rats	- 1 mL of 1% acetic acid	↓ Analgesic activity	[87]
Carrageenan-induced male and female Swiss albino rats	- 400mg/kg for 4 hours	↓ Edema volume	[88]
LPS-induced female C57BL/6 mice	- 20 mg/kg for 2 days	↓ IFN-γ concentrations in the blood serum ↓ Albumin denaturation ↓ Enzyme release	[89]

8. Clinical Studies on the Effect of *Phyllanthus niruri* in Metabolic Syndrome

Sowjanya et al. reported that in a block-randomized, double-blind, parallel-arm, placebo-controlled trial with 454 patients, including 100 patients with alcoholic hepatitis, *P. niruri* treatment for 4 weeks significantly reduced AST, ALT, ALP, GGTP, and bilirubin levels, with an increase in albumin levels. TC and TG levels also decreased as total antioxidant activity increased. *Phyllanthus niruri* also improved renal parameters by reducing creatinine and uric acid levels [90]. Hassan MRA et al. reported that in a 12-month, randomized, double-blind, placebo-controlled study involving 267 patients, 112 received Phyllanthus niruri and 114 received a placebo. The treatment decreased liver biomarker levels (AST, ALP, GGT, ALT) with no change in the AST/ALT ratio & CAP score. Besides, it also reduced the fibrosis score, with no change in HDL & slightly decreased levels of LDL and Total Cholesterol (TC) [91].

Shaker et al. reported that, in a randomized, double-blind, placebo-controlled, three-arm, interventional trial, 146 patients with non-alcoholic steatohepatitis were treated with *P. niruri* for 36 weeks, and the treatment

significantly reduced ALT and AST levels, CAP score & FAST score [92]. Besides, there was no change in KP_a and FIB-4 score. *Phyllanthus niruri* treatment also lowered lipid profile biomarkers (HDL, LDL, TG) levels [92]. Khan MN et al. reported an open-label, randomized controlled trial in which 68 adult patients with alcoholic liver disease received *Phyllanthus niruri* treatment for 12 weeks, and after treatment, levels of liver biomarkers (total bilirubin, direct bilirubin, SGOT, SGPT, ALP, GGT, and MELD score) decreased significantly. His study reported reduced serum albumin and globulin levels after treatment [93]. Kumar et al. reported a 12-week, double-blind, randomized, active-controlled, multicenter, prospective trial in which 132 adult patients with liver disease received a *P. niruri* tablet, and ALT, AST, ALP, TB, and direct & indirect bilirubin levels were dramatically reduced [94]. All the other liver function tests: total proteins, albumin, AG ratio, and PT/INR ratio remained within the normal range, with their levels lowered [94]. Shaker et al. reported a phase II, multicenter, randomized, double-blind, placebo-controlled, and three-arm interventional clinical trial that was conducted in patients for 36 weeks with apparent risk factors for non-alcoholic steatohepatitis (NASH) [95]. The product, Heptex, consists of *Phyllanthus niruri* and *Silybum marianum. Phyllanthus niruri* tablet capsule 200mg and *Silybum marianum* capsule 100 mg. *P. niruri* capsule was in a higher dose, and Silybum marianum was in a lower dose [95]. Then, ALT and AST decreased in both the low- and high-dose groups. TC showed a significant change in the low-dose group, whereas HDL, LDL, and TG did not change. The CAP score decreased, and there was no significant change in the Fib-4 score or liver stiffness with a lower FAST score [95].

Sowjanya et al. mentioned a Phase II clinical trial, a block-randomized, double-blind, parallel-arm, placebo-controlled study, conducted in patients with mild to moderate alcoholic hepatitis. After *Phyllanthus niruri treatment,* total antioxidant levels and appetite increased significantly [96]. There were no significant changes in AST, ALP (liver enzymes), GGT, bilirubin, albumin, INR, urea and creatinine, TG, TC, and oxidant levels [96]. Hassan et al. conducted a randomized controlled, double-blind, placebo-controlled, parallel-group trial in patients with mild to moderate non-alcoholic fatty liver disease (NAFLD) [97]. The treatment was 250mg of *Phyllanthus niruri* for 12 months. The treatment showed a significant reduction in the fibrosis score and improvements in AST, ALT, AST/ALT ratio, and CAP score. The treatment was well-tolerated and showed a potential antifibrotic effect. Moreover, less effect on steatosis and metabolic markers [97].

Table-6 Effects of *Phyllanthus niruri* in clinical studies

Study type	Dose& Duration	Results	Ref.
Block randomized, double-blind, parallel-arm placebo-controlled trial (100 alcoholic patients)	500 mg tablet twice daily for 4 weeks	↓ AST, ALT, ALP, GGTP, Bilirubin ↑ Albumin, ↑creatinine, Urea. ↓ TC, TG. INR ↓ total oxidant, total antioxidant.	[90]

Randomized, double-blind, placebo-controlled trial (112 non- alcoholic patients)	Hepar-P capsule (250mg) twice for 12 months	↓ ALP, GGT; AST, ALT, CAP score, AST/ALT: no change ↓Fibrosis, HDL: no change, ↓LDL, TC.	[91]
Randomized, double-blind, placebo-controlled, three-arm, interventional trial (146 non-alcoholic steatohepatitis patients)	Heptex^{R} capsules (200 mg) three times for 36 weeks	↓ ALT, AST. ↓ CAP, FAST. KP_a, FIB-4: no change. ↓ HDL, LDL, TG.	[92]
Open-label, randomized controlled trial (68 adult ALD patients)	BoozLiv^{TM} syrup twice daily for 12 weeks.	↓ TB, DB, SGPT, SGOT, ALP, GGT, MELD score. ↓ serum albumin, serum globulin.	[93]
Double- blind, randomized, active-controlled, multicenter, prospective (132 adult liver disease patients)	Hepano tablet for 12 weeks	↓ AST, ALT, ALP, TB, Direct & indirect bilirubin. ↓ TP, albumin, AG ratio, ↓ PT/INR ratio.	[94]
PhaseII, Multicenter, Randomized, Double-blind, Placebo-controlled,Three-arm interventional clinical trial.Conducted in patients with apparent risk factors for non-alcoholic steatohepatitis (NASH)	PN capsule 200mg and SM capsule 100 mg for 36 weeks	↓ ALT , AST decreased in low and high dose group TC significant change in low dose group HDL,LDL, TG no changes ↓ CAP score No significant change in Fib-4 score and liver stiffness ↓ FAST score	[95]
Phase II clinical trial, Block-randomized,	500mg capsule twice daily for 4 weeks	Total antioxidant levels and appetite increased significantly	[96]

Double-blind, Parallel-arm, Placebo-controlled, Conducted in patients with mild to moderate alcoholic hepatitis		No significant change in AST, ALP (liver enzymes), ALP,GGT, Bilirubin, albumin, INR, Urea and creatinine, TG, TC, and oxidant levels	
Randomized controlled trial, Double-blind, Placebo-controlled, Parallel-group, Duration: 12 months (1 year), conducted in patients with mild to moderate non-alcoholic fatty liver disease (NAFLD)	250mg PN for 12 months	Significantly reduced fibrosis score Improvement in AST, ALT, AST/ALT ratio and CAP score Well tolerated and potential antifibrotic effect Less effect for steatosis and metabolic markers	[97]

9. Toxicological Perspectives for *Phyllanthus niruri* treatment

Despite the promising pharmacological activities of *Phyllanthus niruri*, its long-term safety and toxicological profile require further systematic investigation before its widespread therapeutic application. Although traditional use and available clinical studies suggest reasonable tolerability, the safety evidence remains insufficient to establish a definitive therapeutic window, particularly for prolonged administration and higher doses. Variations in extraction methods, phytochemical composition, dosage, and treatment duration may influence its biological activity and potential toxicity.

Furthermore, the possibility of herb-drug interactions warrants careful consideration, especially in patients with obesity-related comorbidities who frequently receive antidiabetic, antihypertensive, and lipid-lowering medications. Comprehensive toxicological evaluations, including acute, subacute, and chronic toxicity studies, genotoxicity, reproductive toxicity, and organ-specific safety assessments, are necessary to identify potential adverse effects and establish safe exposure limits. Particular attention should be paid to hepatic, renal, hematological, and metabolic parameters, as well as histopathological examination of vital organs. Establishing standardized extracts with well-characterized phytochemical profiles and conducting systematic pharmacovigilance studies will be essential to ensure product consistency, minimize potential risks, and support the safe translation of *P. niruri* into clinical practice.

10. Future Directions of Research for *Phyllanthus niruri* Treatment

Future research should focus on bridging the gap between promising preclinical findings and clinically validated therapeutic applications of *Phyllanthus niruri* in obesity and its associated metabolic complications. Although existing studies demonstrate beneficial effects on body weight, lipid metabolism, glucose homeostasis, oxidative stress, inflammation, and hepatic and renal function, the precise molecular mechanisms underlying these effects remain incompletely understood. Further investigations employing multi-omics approaches, including transcriptomics, metabolomics, lipidomics, and proteomics, could provide deeper insights into its regulatory effects on metabolic signaling pathways, particularly AMPK, SIRT1, Nrf2/HO-1, NF-κB, and PPAR-related pathways. Future studies should also prioritize the identification and isolation of bioactive constituents, standardization of plant extracts, pharmacokinetic characterization, dose optimization, and evaluation of potential synergistic effects with established therapeutic agents.

Importantly, well-designed, randomized, double-blind, placebo-controlled clinical trials involving larger and more diverse populations are required to establish its efficacy, safety, optimal dosage, and long-term therapeutic benefits in obesity, type 2 diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD), and chronic kidney disease. Integrating mechanistic investigations with rigorous clinical evaluation will be crucial for determining the translational potential of *P. niruri* and advancing its development as a scientifically validated phytotherapeutic intervention for obesity and its related complications.

11. Conclusion:

There is a growing body of scientific evidence supporting the therapeutic potential of *Phyllanthus niruri.* All these results from the cited reviews show that *P. niruri* exhibits a wide range of pharmacological activities, including anti-obesity, hypolipidemic, antidiabetic, hepatoprotective, nephroprotective, antioxidant, and anti-inflammatory effects. Experimental studies have shown that *P. niruri* can improve lipid metabolism, reduce body weight gain, enhance glucose homeostasis, suppress inflammatory mediators, and protect hepatic and renal tissues from pathological damage. These beneficial effects are mediated through the modulation of multiple molecular pathways involved in inflammation, oxidative stress, fibrosis, and metabolism.

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