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REVIEW ARTICLE

Alternative Approaches to Ameliorate Nonalcoholic Fatty Liver Disease: *Phyllanthus niruri* Clinicopathological Significance; A review

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the major global health issues, strongly correlated with metabolic disorder, insulin resistance, obesity and oxidative stress. It is characterized by an excessive accumulation of liver fat, inflammation and dysfunction of the hepatocytes. NAFLD predisposes to cirrhosis, cardiovascular disease, and hepatocellular carcinoma in susceptible individuals. Although the specific signals remain poorly understood, NAFLD pathogenesis can involve the behavior of different types of hepatic cells and several extra-hepatic signals. The difficulty of NAFLD has been a big impediment to advancement and effective therapies with appropriate indicators. NAFLD's alternative medicines with medicinal herbs become the most useful solution today because of their minimum side effects. Phyllanthus niruri (P. niruri) is an herbal medicine that contains various bioactive phytochemicals with hypolipidemic, antioxidant, detoxifying, antimutagenic, anti-inflammatory and antiviral activities. The reduction of fatty acids and decreased insulin resistance (IR) is expected after P. niruri administration, which helps in the prevention of NAFLD. In this review, we describe recent clinical and diagnostic methods examining the diagnosis, development, and effects of NAFLD; comparing the attributes of the genetic and dietary animal models of NAFLD; and highlighting the potential hepatoprotective function of P. niruri, plus its therapeutic role in the prevention of NAFLD.

Keywords: Nonalcoholic fatty liver disease, liver enzymes, lipid profile, *Phyllanthus niruri*.

Introduction

Liver is the main metabolic organ which has an important role in regulating fat, carbohydrate and protein metabolism within the body [1]. Fatty liver is defined as intrahepatic triacylglycerols (TAG) of at least 5% of liver weight or 5% of hepatocytes containing lipid vacuoles in the absence of a secondary contributing factor such as excess alcohol intake, viral infection, or drug treatments. Simple accumulation of TAG in the liver could be hepatoprotective; however, prolonged hepatic lipid storage may lead to liver metabolic dysfunction, inflammation, and advanced forms of nonalcoholic fatty liver disease [2]. Fatty liver occurs due to the presence of TAG-rich microvesicular and or macrovesicular lipid droplets in liver cells, resulting in excessive lipid retention within a cell. Disruption in the fat metabolism predisposes to excessive amounts of fat in the liver which results in a fatty liver [3].

The fatty liver disease could be classified as alcoholic (AFLD) and nonalcoholic (NAFLD), where both showing macrovesicular and microvesicular fatty changes [4].

In general, NAFLD is recognized as the leading cause of chronic liver disease worldwide [5]. NAFLD encompasses varieties of hepatic conditions characterized by inflammation, excessive accumulation of hepatic fat, and dysfunction of liver cells. NAFLD is growing in prevalence parallel to high incidence rates of obesity, metabolic disorders such as diabetes mellitus type II and insulin resistance [6, 7].It might be predisposed to hepatocellular carcinoma, cirrhosis, and cardiovascular disease [8]. Several factors might predispose to the

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development of NAFLD including some types of medications, and nutritional status. Several forms of liver pathologies ranged from basic or uncomplicated steatosis to cirrhosis, advanced fibrosis, HCC (hepatocellular carcinoma), and Nonalcoholic steatohepatitis (NASH) might be implicated behind NAFLD [9].

Still, the major factor responsible for the development of NAFLD is a nutritional lifestyle including inadequate diet such as the high concentration of cholesterol, increased saturated fat, poor fibers, poor vitamins and the presence of external contaminants or xenobiotics [10]. Some researchers provide an idea about the relationship between NAFLD and diet composition such as the atherogenic diets, high-fat with high-cholesterol diet, by adding over amount of fat and cholesterol to standard rat pellet chow. The use of such diets can predispose to liver steatosis, hepatocyte ballooning, necrosis, steatohepatitis and fibrosis within one month [11]**,** Where the addition of fructose and sucrose 10% on drinking solution for 60 days can induce steatosis [12].

In the current review we aimed to highlight the problem of NAFLD and the hepatoprotective role of *P. niruri*. First, we focused on NAFLD pathophysiology, diagnostic markers, and progression of the disease. In addition, we discussed the role of *P. niruri* and its predicted hepatoprotective effect in regard to its pharmacological and anti-inflammatory activities which might play a role to overcome NAFLD.

NAFLD pathobiology

NAFLD and liver enzymes

NAFLD can cause liver injury which lead to fibrosis in the absence of other etiologies of liver disease such as medications, viral hepatitis, and substantial alcohol utilization [13]. NAFLD may predispose to mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), up to 3 times above the greater normal boundary if the supplementary causes are absent [14]. There is no single biochemical marker that can confirm a diagnosis of NAFLD or distinguish between steatosis, NASH, and cirrhosis. Increased serum gamma-glutamyltransferase (GGT) levels have also been shown to be associated with advanced fibrosis in NAFLD patients [15]. Although mildly elevated serum aminotransferases activities are the primary abnormality seen in patients with NAFLD, liver enzymes may be normal in up to 78% of patients with NAFLD [16]. Serum level of GGT, alkaline phosphatase (ALP) or both are frequently elevated in NAFLD [17].

NAFLD and lipid profile

A significant relationship was seen between lipid profile and NAFLD. There is a higher TC/HDL ratio and TC, LDL/HDL ratio and lower HDL in the NAFLD individuals matched with the non-NAFLD individuals [9]. Dysregulation expression of glucose and lipid metabolism-related genes induced by chronic high-fat diet can lead to augmented serum TG content, cholesterol and fasting plasma glucose (FPG) concentrations [18].

NAFLD and Insulin resistance

A potential risk factor for NAFLD is known to be insulin resistance. Several studies have shown that NAFLD is associated with insulin resistance, leading to an increase in free fatty acids (FFAs) resistance to the antilipolytic effect of insulin in adipose tissue. The increase of FFAs induces mitochondrial dysfunction and development of lipotoxicity. Moreover, in subjects with NAFLD, ectopic fat also accumulates as cardiac and pancreatic fat [19]. In the insulin-resistant adipose tissues, high fat intake induced an elevation in the lipolysis rate that lead to increased levels of blood free fatty acid (FFAs). These FFAs can impair mitochondrial β-oxidation in the insulin-resistant liver. High consumption of carbohydrates in the diets with insulin resistance contributes to channeling of further glucose through the liver, where it is transformed to FFAs or glycogen by means of insulin-stimulated de novo lipogenesis [20].

Insulin resistance caused an elevation in serum FFAs by hastened the lipolysis in the peripheral adipose tissue and visceral fat. Peripheral insulin resistance has induced hyperglycemia and it also facilitates fatty acids synthesis in the liver. An elevation of

chylomicrons was observed after ingestion of food containing high concentrations of fats. Peripheral insulin resistance is often accompanied by elevated insulin levels, which inhibit very low-density lipoprotein formation (VLDL) [21].

NAFLD and immunity

Dysfunction of immune system along with inflammatory pathways is involved in the NAFLD development [22]. In the pathogenesis of nonalcoholic steatohepatitis (NASH), neutrophils, natural killer (NK) cells, kupffer cells (KCs) and dendritic cells play a significant role. Hepatic cell oxidative damage caused by neutrophils activation increases the production of pro-inflammatory cytokines and contributes to oxidation [23]. Kupffer cells (KCs) are activated in chronic or acute liver disease and, through this activation of KCs, which trigger T cells and induce hepatocyte apoptosis, increase pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and (IL-1b). In addition, natural killer (NK) cells are abundant in the liver tissue and have an anti-fibrotic effect in the liver, and reduction of the activity and levels of NK cells can increase liver cirrhosis susceptibility among obese individuals [24]. Natural killer (NK) cells therefore play a role in the development of liver injury and fibrosis, and decrease the development of NASH and NAFLD [25].

The complement system has a central molecule which is called complement C3. Some studies demonstrated that serum C3 levels are related to a higher prevalence of NAFLD and AFLD in an adult population. The prevalence of NAFLD and its severity were positively associated with higher levels of serum complement C3 [26, 27]. The potential role of complement fraction C3 as a biomarker of NAFLD in the general population has been indicated by recent data. Complement system activation has been shown in liver biopsies from patients with NAFLD compared to healthy control [28].

Genetic factors in correlation to NAFLD

Newly identified genetic risk variants could provide a useful tool for the clinical management and prognosis of patients with NAFLD. They may also lead to the identification of drugs for treating NASH, a condition for which specific pharmacological treatment is still lacking [29]. The mechanism which underlying cardiovascular risk in patients with NAFLD is more complex and includes both genetic mechanisms associated with the metabolic syndrome and other related to NAFLD [30] Patatin-like phospholipase domain containing 3 (PNPLA3) gene, which also named adiponutrin, is expressed in the intracellular membrane fractions of the liver cells and has a molecular mass of 53 kDA approximately in humans [31, 32]. PNPLA3 gene encodes is expressed in the liver with an expression ten times greater than that of adipose tissue [31]. There is an association between the elevated level of PNPLA3 and the incidence of NAFLD in obese Egyptian patients [33].

Histological changes in NAFLD

The percutaneous liver biopsy is the general standard for the diagnosis of NAFLD, although it is not accepted by patients and even by doctors, it considers the most accurate diagnostic tool.

Histologically (Figures 1-4), the fatty liver will be detected by the fat accumulation in the pericentral (centrilobular) zone [34-37]. The presences of fatty change with the hepatocytes which contain several large fat droplets lead to displacement of the nucleus. The lipid deposits may be released because of the rupture in distended liver cells and produce lipid granuloma which are composed of occasional lymphocytes and chiefly of macrophages [38].

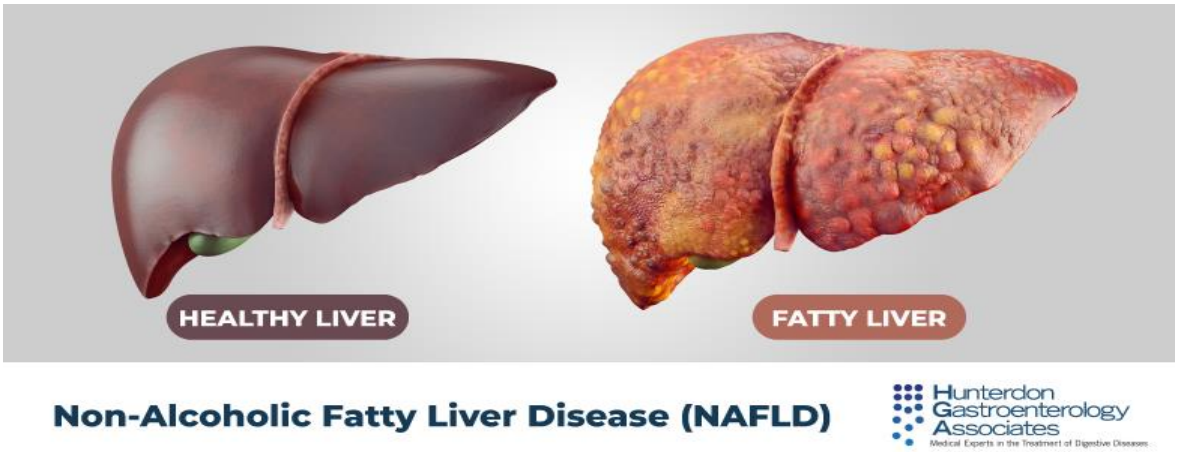

Figure (1): Nonalcoholic fatty liver disease. Liver was showed enlarged and yellowish in color (Figure cited from Non-Alcoholic Fatty Liver Disease (NAFLD) Hunterdon Gastroenterology Associates | Digestive Health Specialists - Flemington, NJ).[the figure is cited from Mayo Clinic, 2018 , Aug. 2018. Non-alcoholic Fatty Liver Disease. [34].https://hunterdongastro.com/non-alcoholic-fatty-liver-disease-nafld/

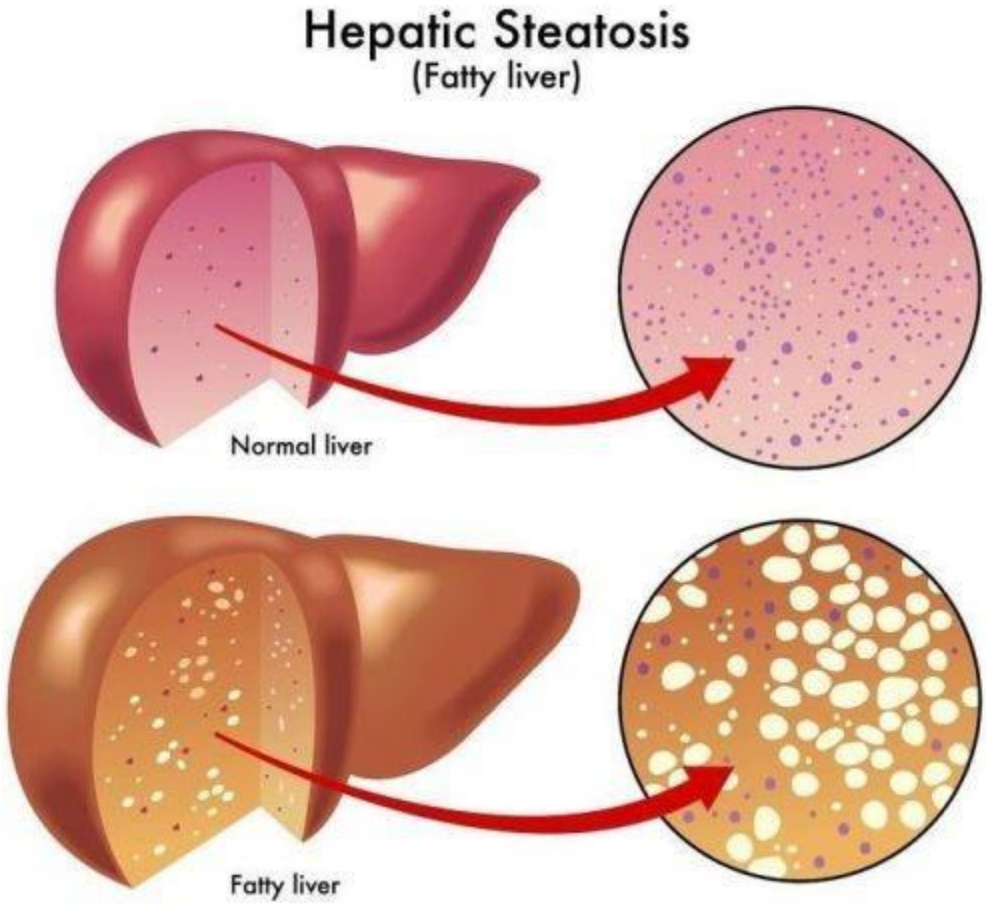

Figure (2): Digramatic distribution of fat dropleps in nonalcoholic fatty liver disease. Fat droplets were showed in liver hepatocyte. (Figure cited fromtransplantliverinindia.com). Book: Mayo Clinic Family Health Book, 5th Edition, 2016. [35]. https://ar.medicineh.com/85-fatty-liver-disease-22890

Nonalcoholic steatohepatitis (NASH), the severe form of NAFLD, can progress to liver cirrhosis and hepatocellular carcinoma. Although noninvasive clinical scores and image-based diagnosis for NAFLD have improved, histopathological evaluation of

biopsy specimens remains the gold standard for diagnosing NAFLD/NASH. Steatosis, lobular inflammation, and hepatocellular ballooning are all necessary components for the diagnosis of NASH; fibrosis is also typically observed. Other histopathological abnormalities commonly observed in NASH include hepatocellular glycogenated nuclei, lipogranulomas, and acidophil bodies [39].

Alternative approaches for NAFLD

Nonalcoholic fatty liver disease (NAFLD) refers to a variety of liver diseases from hepatic steatosis to NASH and liver cirrhosis. NAFLD is also observed in obese people and is often linked to metabolic changes such as systemic insulin resistance. Hepatic steatosis can result in oxidative hepatocellular damage, inflammation, and activation of fibrogenesis in susceptible individuals, namely, NASH [29, 40]. The treatment of NAFLD patients targets metabolic syndrome elements, lifestyle change, and liver-driven pharmacotherapy for patients with elevated risk and handles cirrhosis complications. The high caloric diet with increased fat or high carbohydrate intake contributed to the prevalence of NAFLD. Lifestyle modification is directed towards the increased activity and weight loss that is effective for the prevention of NAFLD [41].

Histology of the liver can be improved by weight loss but it cannot improve fibrosis of the liver. The macronutrient diet composition should nevertheless be used to lose weight or directly boost NAFLD without weight loss. A study with a diet low in fat, particularly in saturated fatty acids, and low in refined carbohydrates, particularly by reducing consumption of soft drinks, in patients with NAFLD, proved the nutritional factors may play a major role in NAFLD**.** By diminishing dietary fat content, the liver fat content changes within 2 weeks. Without any change in body weight, intra-abdominal or subcutaneous fat mass, fatty acid concentration, carbohydrate, lipid or protein oxidation rates, all increases in liver fat content occurred. Changes in liver fat content have been followed by increases in fasting serum insulin levels. The combination of dietary macronutrient composition with NAFLD is therefore extremely important and can provide new nutritional approaches to slow the development of non-alcoholic fatty liver disease [42].

Traditional herbal medicine (THM), is an important source for the development of hepatoprotective drugs [43]. Traditional Chinese medicine (TCM) reduces radiological steatosis, ALT and AST activities and thereby benefits from NAFLD prevention, indicating that traditional Chinese medicine (TCM) has a useful role in NAFLD relief in 62 patients out of 419 clinical trials [44]. Natural polyphenol that activates sirtuin 1 (SIRT1) has powerful effects on NAFLD improvement in both rodent and in vitro cellular studies, although its role in patients with NAFLD is still inconclusive [45]. Berberine (BBR) is a natural alkaloid found in Coptis Chinensis and many other herbal medicinal products of China. It showed several pharmacological and biological effects in a series of metabolic diseases including NAFLD. BBR is reported to inhibit cholesterol and triglyceride synthesis in human hepatoma cell line (HepG2) cells and primary hepatocytes. In vivo data from various animal models also confirm BBR's beneficial role in preventing or treating NAFLD [46].

Some studies shed light on the phytotherapy against NAFLD, among which silymarin (SIL) drives people to investigate most. SIL, extracted from the fruit and seeds of the *Silybummarinum* (milk thistle), contains a family of flavonolignans (silybin, isosilybin, silychristin, isosilychristin, and silydianin) and a flavonoid (taxifolin), among which silybin accounts for 50% to 70% of the extraction and is identified as major biologically active component. Recently, SIL extract tablets treated fatty liver disease in several clinical trials, whose results showing decreased hepatic enzymes levels in serum, especially ALT, indicated that SIL could partially restore the liver's function and mitigated NASH patients' symptoms [47].

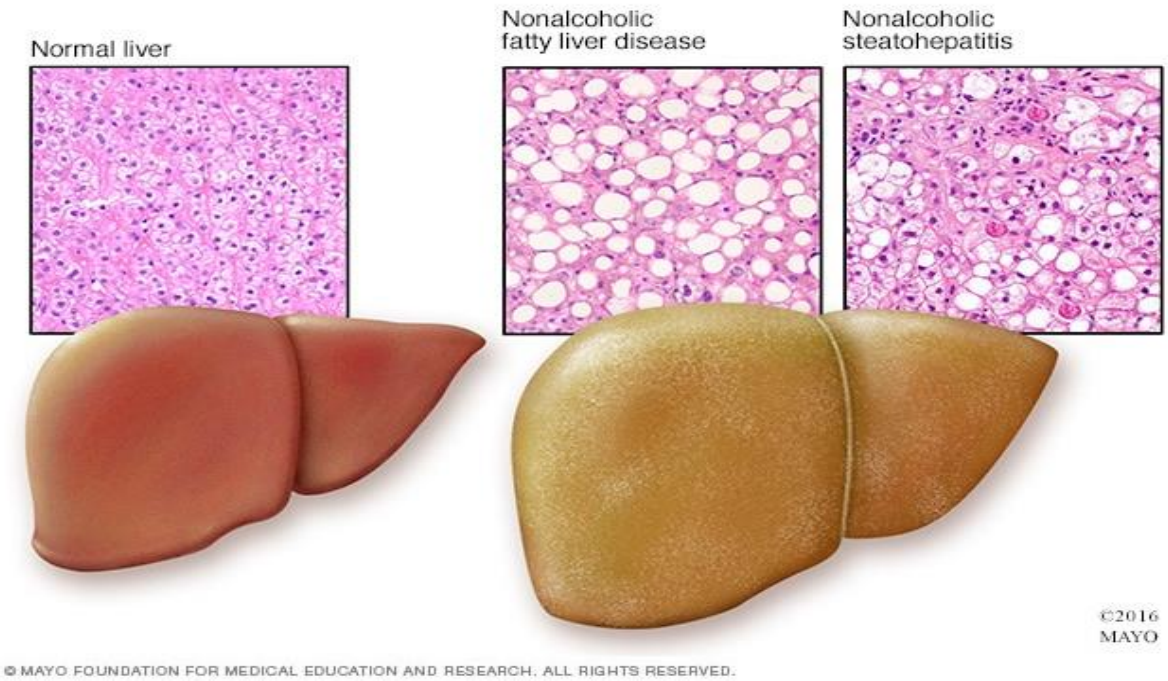

Figure (3): Nonalcoholic fatty liver disease. Compared with a normal liver (left), a fatty liver (right) appears enlarged and discolored. Tissue samples reveal fat deposits in nonalcoholic fatty liver disease, while inflammation and advanced scarring (cirrhosis) are visible in nonalcoholic steatohepatitis. (Figure cited from Book: Mayo Clinic Family Health Book, 5th Edition, 2019) [36]. https://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/symptoms-causes/syc-20354567

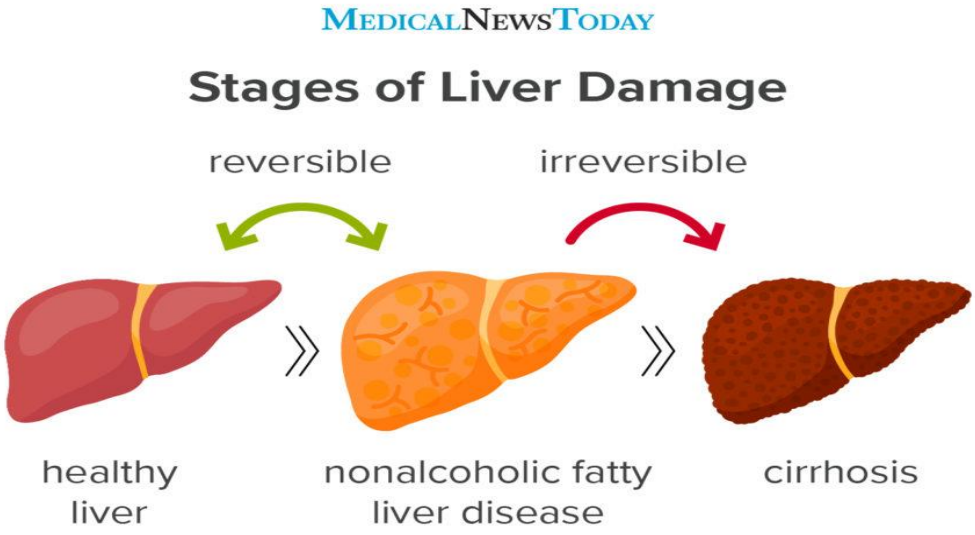

Figure (4): Nonalcoholic fatty liver disease. Liver was showed stages of liver damage (Figure cited from Medical news today 2020). [37]. https://www.google.com.eg/search?q=stages+of+liver+damage&tbm=isch&hl=ar&safe=active&chips=q:alcoholic+hepatitis+stages+of+liver+damage,online_chips:alcoholic+hepatitis,online_chips:nonalcoholic+fatty&sa=X&ved=2ahUKEwjOp6TF1IftAhUPChQKHUJRASAQ4lYoAXoECAEQGA&biw=1263&bih=657#imgrc=OBW7AqkNTGNneM

Phyllanthus niruri and its therapeutic uses

Phyllanthus niruri described as the herb which is quite glabrous; stem often branched at the base, 30-60 cm in height (Figure 5). Leaves are numerous, sessile distichously often imprecating. Flowers is elliptical elongated yellowish, very numerous, axillary. The female flowers are solitary in nature while the male flowers are one to three in number. Capsules have a diameter of 2.5 mm, depressed globes, and flat barely lobbed [48]. *P. niruri* Linn. belongs to the *Euphorbiaceae* family and it is a small herb having wide range of medicinal properties, and it is used widely across the world. Its taste is bitter, shows a laxative effect and acts as astringent [49]. *P. niruri* is growing in subtropical and tropical regions around the world. *P. niruri* grows as a weed in moist lands. It is commonly used in therapeutic applications by many countries [50]. This plant is originated in India that is used in the prevention of ulcers, jaundice, diabetes, skin diseases, urinary complications, and chest pain [49] and also it is widely distributed in East South Asia, which is used to treat chronic hepatitis [52]. The scientific investigation discovered that *P. niruri* has potent activity against various diseases such as HIV, hepatitis B, microbial infections, nematode infestation, plasmodiasis, hyperlipidemia, lithiasis, hyperuricemia, diabetes, nephrotoxicity, radiation exposure, platelet aggregation, unwanted pregnancy, algesia, vasoconstriction, biological oxidation, and hepatotoxicity [50].

P. niruri has curative effects due to the presence of bioactive phytochemicals such as alkaloids, lignans, terpenoids, polyphenols, coumarins, tannins, saponins, flavonoids, hypophyllanthin, phyllanthin, and glycosinoids [49, 53]. These phytochemicals are responsible for the pharmacological activity of *P. niruri*. The phytochemicals and pharmacological properties of the medicinal herb *P. niruri* are diverse. Aqueous extract of *P. niruri* have a wide range of therapeutical activities such as a diuretic, antimicrobial, hepatoprotective, antiviral, anticancer, antioxidant, anti-inflammatory, antiplasmodial, antidiabetic, lipid-lowering action and antifungal [49,53].Methanolic extract of *P. niruri* exhibited immunomodulatory activity and anti-HIV activity [54]. In spite of its wide range of uses from an ethnomedicinal point of view, research on most of these possible therapeutic applications has not reached the stage of clinical trials. The majority of pharmacological strategies include using antioxidant agents and insulin sensitizers, and also reducing the effect of dietary carbohydrate and fats by the inhibition of cholesterol micellization, pancreatic lipase and α-glucosidase [55].

Figure (5):*Phyllantus niruri* plant showing annual herb is 30-60 cm high, quite glabrous, stem often branched at the base. Leaves are numerous, elliptic oblong Flowers, [the figure is cited from Prajapati *et al.* [48].

Pharmacological activities of *Phyllanthus niruri*

The lipid-lowering activity of Phyllanthus niruri

The percentage of fat within the hepatocytes determined the degree of hepatic steatosis which graded from grade 0 (healthy, <5%) to grade 3 (severe, >66%) [3]. Firstly, TAG synthesis and accumulation in the liver are considered hepatoprotective; however, under the stressed condition such as abnormal lipid metabolism, obesity or high fat/high carbohydrate intake, the ectopic hepatic lipid accumulation has happened easily. NAFLD is associated with increased triglyceride (TG), ApoB, concentrations of low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) [17]. The lipid lowering activity of *P. niruri* has been studied in triton and cholesterol fed hyperlipemic rats [54]. The histology or imaging methods can be used to ensure an excessive load of triglycerides in the hepatocytes [14].

Phyllanthus niruri have bioactive components ellagic acid and phyllanthin which have antioxidant and hypolipidemic effects that play an essential role in therapeutic properties to ameliorate NAFLD. *P. niruri*'s powerful therapeutic impact as a natural source of NAFLD treatment was high. The most numerous and widely distributed class of phytochemicals are polyphenols which include lignans, chromones, xanthones, coumarins, stilbenes and flavanoids. Flavanoids have relatively effective anti-inflammatory, anti-oxidant, anti-atherosclerotic, anti-mutagenic, anti-tumor and, anti-viral activities [21]. Another study explains the action of saponins and alkaloids in decreasing the levels of lipids and cholesterol [56]. *P. niruri* administration at a dose of 200 mg/kg BW. for 1 month in rats fed with cholesterol resulted in significant decreased levels of total cholesterol, phospholipid, low-density lipoprotein and triglyceride by 24, 25 and 27 % respectively [57]**.**

Immunomodulating effects of Phyllanthusniruri

P. niruri as an immunomodulator has scientifically been studied and evaluated in different clinical trials for the treatment of chronic hepatitis B, pulmonary tuberculosis, vaginitis, as well as varicella-zoster infection. In such diseases, the effective immune system is crucial to the treatment success and eradication of the pathogens. In those clinical studies, *P. niruri* has been proven for its capacity to modulate and activate the immune system [58].

An aqueous extract of *P. niruri* demonstrated high stimulation and mitogenic activities on experimental animals' lymphocytes and macrophages at a dose of 12.5–200 μg/ml [59]. In addition, a pre-clinical study explained the ability of *P. niruri* extracts at a dose of 50–200mg/kg BW to reduce the cellular and humoral immune responses [60].

P. niruri has been shown to have anti-bacterial and anti-viral effects, including against *Staphylococcus aureus* and *Streptococcus agalactiae* [61]. In addition, extract of *P. niruri* has been observed to induce macrophage activity by increasing phagocytosis and nitric oxide (NO) in mice macrophage infected with *Salmonella typhii* and in the macrophages of tuberculosis patients [62].

Detoxification and antioxidant activities of Phyllanthus niruri

Phyllanthus niruri has high percent of flavonoids and phenolic compounds that are responsible for its potent antioxidant properties, which could play important roles in hepatoprotective activity [63]. Aqueous *P. niruri* extract administration to diabetic Wistar rats, not only normalized the activity of endogenous antioxidants and levels of plasma vitamin C and vitamin E, but also decreased malondialdehyde (MDA) lipid peroxidation rates [64]. In *P. niruri*, 50 per cent methanol extract (ME), the highest total flavonoid and phenolic content was found. In addition to raising the levels of reduced glutathione (GSH) and increasing the activity of endogenous antioxidants superoxide dismutase (SOD) and catalase (CAT) in rat liver , kidney, heart and brain tissues, methanolic extracts of *P. niruri* decreased the levels of TBARS (thiobarbituric reactive substances) in

streptozotocin-induced diabetic rats. Antioxidants can fight free radicals in the body which make cell damage and lead to the disease. Treatment of diabetic male rats with *P. niruri* leaf aqueous extract (200 and 400 mg/kg BW) for 28 consecutive days prevents the increase in the amount of lipid peroxidation (LPO) product, MDA, and the diminution of SOD, CAT, and glutathione peroxidase (GPx) activity levels in the kidney of diabetic rats[65]. A 50% methanolic extract (50% ME) of *P. niruri* exhibited the highest inhibitory effect against NAFLD progression. It significantly reduced hepatomegaly (16%) and visceral fat weight (22%), decreased NAFLD score, prevented fibrosis, and reduced serum MDA (40%) compared to a non-treated high fat diet group [55].

Anti-inflammatory, Antispasmodic and pain-relieving properties of Phyllanthusniruri

Recent studies confirm the anti-inflammatory, antinociceptive, and antipyretic properties of the methanol extract of *P. niruri* in rats and mice due to the isolating compounds that are effective against inflammation and pain [66]. *P. niruri* have the power to heal the wounds by oral or topical administration. It played an important role in wound contraction and epithelialization. It can be used for the treatment of digestive disease, jaundice, renal calculus, hypertension, constipation, skin disease, and fever. When Dexamethasone suppress the wound healing, suppressed rats were treated by *P. niruri* extract which cause an increase in wound contraction by both topical and oral administration [67].

Hepatoprotective activity of Phyllanthus niruri

Liver disease is still a worldwide health problem. Several studies have additionally proven the hepatoprotective effect of *P. niruri* in animal and cell culture models exemplified by the reduction in the levels of liver enzymes.

The bioactive metabolites of *P. niruri* have been isolated from the aqueous extract and the plant's anti-inflammatory properties have been reported as inhibiting COX-2, NF-KB, TNF-alpha, IL-8, IL-6 and IL10 as a potent hepatoprotective mechanism and antioxidant activity. The presence of the polyphenolic compounds in *P. niruri* induces hepatoprotective property [66]. Aqueous extract of *P. niruri* (100 mg/kg b/w) when given orally for 20 days showed hepatoprotective activity in carbon tetrachloride induced hepatic damage in mice. The hepatoprotective effect may be due to the presence of tannin, flavonoids and also may be due to its antioxidant and free radical scavenging properties [68].

Antioxidant activity and hepatoprotective potential of methanolic and aqueous extract of leaves and fruits of *P. niruri* were due to inhibition of membrane lipid peroxidation (LPO), scavenging of 1,1-diphenyl-2picrylhydrazyl (DPPH) radical and inhibition of reactive oxygen species (ROS) in vitro. CCl4 – induced hepatotoxicity in rats, as judged by the raised serum enzymes, ALT and AST, was prevented by pretreatment with the methanolic and aqueous extracts, demonstrating the hepatoprotective action of *P. niruri* [69]. Experimentally administration of *P. niruri* aqueous extract (PNAE) for 2 weeks (200 mg/kg. three times in a week) can induce a significant hepatoprotection against carbon tetrachloride generated hepatotoxicity in mice. The PNAE can be used to restore the total protein levels and marker enzymes to near normal in serum. It can also decrease the high levels of total cholesterol (TC), total lipids (TL), thiobarbituric acid reactive substances (TBARS) and triglycerides (TG) in CCl4 administered mice. This study confirmed the power of the detoxification and cure effect of *P. niruri* [70].

Phyllanthus niruri clinical trials for the prevention of NAFLD

Some studies have recently studied natural phytochemicals used as agents against NAFLD [54]. In this review, the therapeutic effects of *P. niruri* on NAFLD prevention were highlighted. It is reported that hepatomegaly was reduced to 16%, visceral fat weight by 22%, LDL to 65%, serum total cholesterol (TC) by 48%, free fatty acids

(FFAs) by 25%, alkaline phosphatase (ALP) to 38%, ALT to 45%, insulin concentration by 67%, (TC–HDL) /HDL to 64%, LDL/HDL by 66%, MDA to 40%, hepatic content of cholesterol to 43%, and triglyceride to 29% in individuals with NAFLD given *P. niruri* extract with compared to a non-treated group. The more effective dose for the prevention of NAFLD is 1000 mg/kg of 50% ME of PN for 5 weeks. On the other hand, all 50 percent ME doses (250 mg / kg), (500 mg / kg) and (1000 mg / kg) can suppress insulin resistance, decrease ALT and diminish atherogenic ratios [21].

The administration of *P. niruri* leaf extract to the diabetic hyperlipidemic rats showed a marked fall in plasma glucose, total lipids, cholesterol, triglycerides, LDL-cholesterol and VLDL-cholesterol, with increased plasma HDL-cholesterol levels. Also, it resulted in weight gain in hepatic tissue along with an increase in glycogen content by dose of 250 mg/kg B.W. for 6 weeks, so it indicate the potential role of *P. niruri* as an anti-hyperlipaemic agent [63].

P. niruri ethanol extract may be a successful candidate for anti-HCV drug production and can be used as anti-HCV agents. Hypophyllantin and Phyllanthin are the known compounds of *P. niruri* which act against the hepatitis C virus receptor. A strong interaction with 4GAG, a protein involved in the entry stage of HCV, has mediated with both hypophyllantin and phyllanthin. The anti-HCV activity of *P. niruri* extract showed strong inhibition against HCV with IC 50 values of 4.14 µg/mL and yield stronger activity in the entry step of the HCV life cycle [71].

Conclusion

Nonalcoholic fatty liver disease (NAFLD) is a form of triglyceride accumulation within the liver cells. In the absence of alcohol intake, the elevated lipid and carbohydrate diets ingestion is a cause NAFLD. This condition can be diagnosed by abnormal laboratory liver parameters such as elevated liver enzymes and lipid profile. *P. niruri*, a medicinal herb, has several therapeutic uses due to it contains several bioactive phytochemical compounds such as flavonoid, alkaloid, lignans, tannins, saponins, terpenoids, cardiac glycoside, and cyanogenic glycosides. Besides, several important chemical constituents were isolated from *P.niruri* such as ellagic acid and phyllanthin. It has a potent hypocholesterolemic and hepatoprotective activity that can help in suppressing the development of NAFLD. The effective dose of *P. niruri* is 1000 mg/kg for five weeks that can improve liver histopathologic picture, liver weight and weight of visceral adipose tissue.

Conflict of interest

The authors declare that there is no conflict of interest.

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الملـخـص العربى

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مرض الكبد الدهني غير الكحولي (NAFLD) يشمل مجموعة من اضطرابات الكبد التي تتميز بتراكم غير طبيعي للدهون الكبدية والالتهاب واختلال وظائف الكبد. الأهم من ذلك أنه يرتبط ارتباطًا وثيقًا بالسمنة ومتلازمة التمثيل الغذائي.

يعرض مرض الكبد الدهني غير الكحولي الأفراد للإصابة بتشمع الكبد وسرطان الخلايا الكبدية وأمراض القلب والأوعية الدموية. على الرغم من أن الإشارات الدقيقة لا تزال غير مفهومة جيدًا ، فمن المحتمل أن يتضمنمرض الكبد الدهني غير الكحولي إضطرابات لأنواع مختلفة من الخلايا الكبدية وإشارات متعددة خارج الكبد. لقد كان تعقيد هذا المرض عائقا رئيسيا أمام تطوير المقاييس المناسبة لتطوره والعلاجات الفعالة. أصبح العلاج البديل مثل الأعشاب الطبية هو النهج الأكثر فائدة في الوقت الحاضر بسبب الحد الأدنى من آثارها الجانبية.

نبات الاملج هو دواء عشبي يحتوى على العديد من المواد الكيميائية النباتية النشطة بيولوجيًا التي تحتوي على شحميات الدم ، ومضادات الأكسدة ، وإزالة السموم ، ومضادات الطفرات ، الأنشطة المضادة للالتهابات والفيروسات. وقد خلصت الدراسات إلى أن إعطاء الاملج يؤدى الى تقليل الأحماض الدهنية وانخفاض مقاومة الأنسولين ، مما يساعد في الوقاية من مرض الكبد الدهني غير الكحولي .

في هذه الدراسة ، نوضح الطرق التشخيصية الحديثة لتشخيص مرض الكبد الدهني غير الكحولي والتقدم والنتائج ؛ تتم مقارنة مرض الكبد الدهني غير الكحولي والنماذج الحيوانية الوراثية والغذائية ؛ كما تم تسليط الضوء على التأثيرات المختلفة للاملج بالإضافة إلى تأثيره على مرض الكبد الدهني غير الكحولي.