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Investigation of Hepatoprotective Effect of Phyllanthus Niruri Extract in Carbon Tetrachloride-Induced Hepatotoxicity in Wistar Rats

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ABSTRACT

The current research examined the role of Phyllanthus niruri extract in protecting the livers of Wistar rats from carbon tetrachloride (CCl_4)-induced damage. Acute oral toxicity and phytochemical analysis of the hydroalcoholic extract were conducted in accordance with OECD guideline 423. The liver function markers, antioxidant parameters, body weight and histopathology of the liver were examined. Both doses reduced liver function markers with no mortality observed in the extract, and antioxidant status was improved in both doses, and in the 400 mg/kg dose, there was a greater improvement in antioxidant status and also there was an improvement in the liver histology in the extract which was similar to silymarin in some of its evaluations. The results show that P.niruri provides more protection to the liver as the dose increases, and this might be because it has antioxidant and cell-protecting properties. More study is needed to figure out if it is safe and works well as a treatment.

Keywords: *Phyllanthus niruri, hepatoprotective activity, carbon tetrachloride, Wistar rats, oxidative stress, antioxidant enzymes, silymarin.*

1. INTRODUCTION

Liver disorders remain a significant health problem worldwide, as people are exposed to a growing number of chemicals in the environment and therapeutic agents and other insults which harm cells via oxidative pathways [1]. Worldwide, hepatic disease accounts for an estimated two million deaths each year through complications of cirrhosis, viral hepatitis and hepatocellular carcinoma. India already has a serious problem with hepatitis B and C infections, and it's becoming worse due to factors including rising rates of alcoholism, obesity, and diabetes as well as hepatotoxic medication exposure (such as antitubercular medicines) and pollution [2].

The liver is the primary organ of metabolic conversion, detoxification, and maintaining internal balance, and therefore is highly susceptible to chemical and oxidative damage [3]. It gets approximately 75% of its blood supply through the portal vein, so it is the first tissue to come in contact with ingested drugs and poisons. The most highly oxygenated region is the close vicinity of the central vein (zone 3) where these hepatocytes contain the highest concentrations of cytochrome P450, and thus are most susceptible to compounds that need metabolic activation to be toxic [4].

Intoxication with carbon tetrachloride has been studied most extensively as a model of hepatic injury in the laboratory [5]. When carbon tetrachloride reacts with oxygen, it creates a very reactive trichloromethyl radical called CCl3, which then forms the trichloromethyl peroxy radical, OOCCl3. This reaction is facilitated by cytochrome P450 isoenzymes, particularly CYP2E1. In the liver, they trigger a cascade of events that culminates in necrosis and apoptosis by peroxiding polyunsaturated fatty acids in cell membranes, which in turn increases cell permeability, cytoplasmic enzyme leakage into blood, and mitochondrial dysfunction [6]. Kupffer cells become activated and secrete mediators (TNF-a, interleukins), bringing an inflammatory component. The lesions are similar to those of human liver disease, presenting high relevance for the screening of hepatoprotective agents.

Treatment of liver disease varies according to the cause and severity, and few of the drugs that are available actually stimulate regeneration or repair of heavily damaged livers; some have only marginal effectiveness but may have unwanted side effects in prolonged use; some are too expensive and inaccessible to most people in developing nations [7]. This has led to more interest in plant-based products that have flavonoids, phenolic acids, tannins, lignans, terpenoids, alkaloids, and saponins. These compounds work together in different ways to help the body [8]. They fight free radicals, stop lipid peroxidation, boost the body's own antioxidants, support cell membrane stability, and reduce inflammation.

Phyllanthus niruri L. A 30-60cm tall annual herb (family Phyllanthaceae), Bhui Amla is used in Ayurvedic and folk medicine for a long time for hepatic complaints, jaundice, renal calculi and urinary infections [9]. It includes parts that are common in each type, like the lignans phyllanthin and hypophyllanthin, flavonoids such as quercetin and rutin, tannins like geraniin and corilagin, and phenolic acids including gallic acid and ellagic acid.These compounds have antioxidant, anti-inflammatory, and cell-protecting effects. However, its ability to protect the liver has not been proven through experiments. The present study, therefore, investigated the biochemical, oxidative and histological changes induced by CCl4 in the Wistar rats to assess the protection potential of a hydroalcoholic extract of P. niruri against silymarin, the reference drug, at two doses [10].

1.1.Objectives of the Study

- To induce liver damage in Wistar rats using CCl4 and validate the injury by measuring the serum ALT, AST, ALP and bilirubin;
- To determine the level of protection that the extract provides compared to toxic and normal controls;
- To evaluate oxidative status by measuring hepatic SOD, catalase and malondialdehyde (MDA);
- To use a microscope to observe the liver's structure and recovery.
- To statistically analyze the response for a dose response relationship and the comparison to silymarin.

2. LITERATURE REVIEW

Ezzat et al. (2020) [11] performed a thorough chemical characterisation of the extract in addition to an animal and cell culture-based mechanistic investigation of the hepatoprotective effects of Phyllanthus niruri. The results showed that polyphenols, ellagitannins, and flavonoids were present. In vitro, the extract lessened toxicity; in vivo, it decreased serum hepatic enzyme activity, enhanced antioxidant enzyme activity, and decreased lipid peroxidation in rats. Some inflammatory and apoptotic markers were also modulated, thus revealing that protection is mediated by more than one mechanism. The authors considered the species as a good candidate for hepatoprotection and its mechanistic antioxidant approach was very similar to that of the present work.

Ifidon and Oriakhi (2018) [12] investigated the effects of a Phyllanthus niruri leaf ethanol extract on CCl4-induced liver damage and oxidative stress in rats. It had a negative effect on hepatic antioxidant levels while raising indicators of lipid peroxidation and hepatic enzymes. Restoring antioxidant status, the leaf extract decreased the increased malondialdehyde and enzyme levels. The authors identified antioxidant mechanisms as the way in which the species is able to resist CCl4 toxicity. It is very relevant to the present study because the plant and the toxicant are the same as used in the present study, and it is discussed in the context of biochemical measurement.

Arshad et al. (2025) [13] included a combination of Phytochemical screening, molecular docking, and assessment of oxidant stress to evaluate the anti-hepatic toxic effects of extracts of Phyllanthus niruri in CCl4-induced hepatic toxic rats. A spectrum of bioactive constituents was identified through screening and protein targets associated with hepatic injury and oxidative damage were shown to be targets of the dock. Both the serum hepatic enzyme activity and antioxidant balance were disturbed through exposure to the toxicant and the extracts were reported as effective in counteracting these. The antioxidant and radical-scavenging properties of the phytochemicals were believed to provide

protection. The study is relevant here as it uses the same animal model and antioxidant endpoints as to the evaluation of Phyllanthus niruri.

Olusanya (2025) [14] looked at how the ethanol extract from Phyllanthus niruri affects high lipid levels that happen because of liver damage caused by CCl4 in Wistar rats. Treatment with the toxicant caused liver damage and changes in the lipid profile of the serum, suggesting a disturbance in lipid handling by the liver. Treatment with the extract was reported to bring ALT, AST and ALP values and the lipid profile back towards normal. The author suggested that hepato-protecting activity of the extract in the rats resulted in the survival of the organ in controlling lipid metabolism, thereby providing additional evidence of its hepatoprotective activity in rats damaged by CCl4.

Shanmugam et al. (2026) [15] evaluated the effect of Phyllanthus niruri on rats of Wistar albino strain with D-galactosamine induced hepatitis, with special emphasis on the parameters for oxidant stress and antioxidant enzyme activity. The toxicant caused extensive liver damage, increase in oxidative load and depletion of the intrinsic defence system. The herb modulated oxidative stress in the liver by raising catalase and superoxide dismutase activity and decreasing liver tissue parameters. The plant's hepatoprotective impact may extend beyond a single chemically produced hepatitis model, according to the authors, who ascribed the protection to the plant's capacity to endure oxidative stress.

3. MATERIALS AND METHODS

3.1. Study Design and Experimental Animals

A study was done to check how well Phyllanthus niruri extract can protect the liver from damage in Wistar rats that had been made sick by carbon tetrachloride. After spending a week getting used to their new environment, adult rats weighing 150–200 g were given free access to water and standard feed in a controlled laboratory setting. Following institutional animal ethics regulations and CPCSEA rules, all study-related activities involving animals were carried out.

3.2. Plant Extraction and Phytochemical Screening

The entire P.niruri plant was checked to confirm its identity, then dried in the shade, ground into a fine powder, and soaked in a mixture of ethanol and water (70 parts ethanol to 30 parts water by volume) using a Soxhlet apparatus to extract the active components. I used a rotary evaporator to concentrate the extract, then dried it and kept it in the refrigerator. The percentage yield was calculated based on the dried extract and the powdered plant material. Qualitative test for alkaloids, flavonoids, tannins, saponins, phenols and glycosides were conducted as preliminary phytochemical screening.

3.3. Acute Toxicity and Experimental Grouping

At the end of the treatment period, blood was drawn, the blood coagulated and centrifuged for 10-15 minutes at 3000 rpm. Diagnostic kits and a semi-automatic analyser were used kinetically to measure the following at 340 nm, 405 nm and 546 nm, respectively: ALT, AST, ALP and total bilirubin, which were stored at −20°C.

Table 1: Experimental Grouping and Treatment Schedule

Group	Name of Group	Treatment	No. of Animals
I	Normal Control	Vehicle only (0.5% CMC, p.o.)	6
II	Toxic Control	CCl_4 (1 mL/kg, i.p., 1:1 in olive oil)	6
III	Low Dose Treatment	CCl_4 + Phyllanthus niruri extract (200 mg/kg, p.o.)	6
IV	High Dose Treatment	CCl_4 + Phyllanthus niruri extract (400 mg/kg, p.o.)	6
V	Standard Control	CCl_4 + Silymarin (100 mg/kg, p.o.)	6

3.4. Biochemical and Antioxidant Analysis

Blood sample was drawn at the end of the treatment period, left to clot and centrifuged at 3000 rpm for 10-15 minutes. Diagnostic kits and a semi-automatic analyser were used kinetically to measure the following at 340 nm, 405 nm and 546 nm, respectively: ALT, AST, ALP and total bilirubin, which were stored at −20°C.

The phosphate buffer with a pH of 7.4 was used to mix the liver tissue, which was 10% of its weight. The levels of SOD, CAT, and MDA were checked in the supernatant. The pyrogallol oxidation method, CAT measured at 240 nm, and MDA measured at 532 nm were used to assess SOD activity.

3.5. Histopathological Examination

Tissue samples from the liver were placed in 10% neutral buffered formalin to preserve them, then processed and placed in paraffin to be embedded. The morphology of the liver was examined by hematoxylin and eosin staining of sections 4–5 µm thick and microscopic examination for hepatocyte degeneration, centrilobular necrosis, fatty changes, inflammatory infiltration, sinusoidal dilatation and vascular congestion. The extent of tissue damage ranged from 0 (normal) to 3 (severe).

3.6. Statistical Analysis

The data were presented using the mean plus or minus the standard error of the mean. To check the differences between the groups, we used one-way ANOVA along with Tukey's post hoc test. For statistical purposes, a p-value below 0.05 was considered significant. The defined percentage of protection was:

The percentage protection (%) = (Toxic control – Treated group) / (Toxic control – Normal control) × 100.:

Percentage protection (%) = [(Toxic control − Treated group) / (Toxic control − Normal control)] × 100.

4. RESULTS AND DISCUSSION

The results of the hepatoprotective activity of Phyllanthus niruri extract are presented in this section, which involves biochemical, antioxidant and histopathological evaluations.

4.1. Extract yield and phytochemical profile

Ethanol–water (70:30 v/v) Soxhlet extraction of 500 g powdered whole plant yielded 62.5 g of dried extract (12.50% w/w). The extract was dark greenish brown in colour, thick, semisolid and slightly sticky with a characteristic herbal odour indicating efficient extraction of polar and semi-polar constituents which was stored in a suitably airtight container in the refrigerator. The amount was sufficient for the phytochemical and pharmacological studies.

All six classes of constituents tested were found (Table 2). The result of flavonoids, tannins and phenols which are all natural antioxidants, reveals the chemical composition for potential hepatoprotective activity against radical mediated damage and anti-inflammatory and cytoprotective activity may be attributed to the presence of alkaloids and glycosides.

Table 2: Preliminary Phytochemical Screening of Phyllanthus niruri Extract

S. No.	Phytoconstituent	Test performed	Observation	Result
1	Alkaloids	Dragendorff's test	Orange precipitate	+
2	Flavonoids	Shinoda test	Pink-red colour	+
3	Tannins	Ferric chloride test	Blue-black colour	+
4	Saponins	Foam test	Persistent froth	+

5	Phenols	Lead acetate test	White precipitate	+
6	Glycosides	Keller–Killiani test	Reddish-brown ring	+

(+ = Present, – = Absent)

4.2. Acute oral toxicity

A single oral dose of 2000 mg/kg produced no appreciable change in general behaviour, skin, fur, eyes, food and water intake, body weight or respiration, and tremors, convulsions, salivation, diarrhoea, sedation, coma and respiratory distress were all absent; there was no mortality during the 14-day observation period. The extract could thus be considered safe at the limit dose, equivalent to an LD50 of more than 2000 mg/kg. The doses of 200 mg/kg and 400 mg/kg were thus chosen, which are one-tenth and one-fifth of the limit dose.

4.3. Effect on body weight

Pre-experimental body weights were not significantly different between groups ($F = 2.12$, $p > 0.05$) which indicated even distribution. Normal control animals gained 16.45 ± 1.34 g (9.95 ± 0.82%), whereas toxic control animals lost 12.60 ± 0.81 g (−6.96 ± 0.51%; final weight 169.3 ± 4.4 g). Treatment with the extract prevented this loss in a dose-related manner, producing gains of 1.98 ± 1.27 g (1.10 ± 0.67%) at 200 mg/kg and 10.98 ± 1.32 g (6.41 ± 0.85%) at 400 mg/kg ($p < 0.001$), the latter comparable with silymarin (10.55 ± 0.81 g; 6.30 ± 0.63%; $p > 0.05$). Toxic group animals might have suffered from liver damage and the change in appetite and metabolic rate after CCl4 exposure could be responsible for the weight loss in this group.

4.4. Effect on serum markers of liver function

The result of the extract in rats administered with carbon tetrachloride is shown in Table 6.5 and Figure 6.1. ALT is a cytoplasmic enzyme which is present in large amounts in the hepatocyte.

Table 3: Effect of Phyllanthus niruri Extract on Serum ALT in CCl_4-Induced Hepatotoxicity

Group	Treatment	ALT (IU/L)	% Protection
I	Normal Control	39.03 ± 2.38	–
II	Toxic Control (CCl_4)	361.88 ± 14.53#	–
III	CCl_4 + P. niruri (200 mg/kg)	168.32 ± 7.46***	60.0
IV	CCl_4 + P. niruri (400 mg/kg)	92.00 ± 4.81***	83.6

V	CCl_4 + Silymarin (100 mg/kg)	73.32 ± 4.12***	89.4

*Mean ± SE, n = 6. #p < 0.05 versus normal control; ***p < 0.001 versus toxic control (one-way ANOVA, Tukey's post hoc test).*

Table 6.5 shows that CCl4 significantly increased serum ALT level from 39.03 IU/L (normal control) to 361.88 IU/L (toxic control), which represents hepatocyte damage. Doses of 200 mg/kg and 400 mg/kg of the extract lowered the value to 168.32 and 92.00 IU/L, equivalent to 60.0% and 83.6% protection respectively ($p < 0.001$), while silymarin brought it down to 73.32 IU/L (89.4% protection). The extract worked well to lower the amount of ALT leaking out from damaged cells, and the more of it was used, the more effective it was.

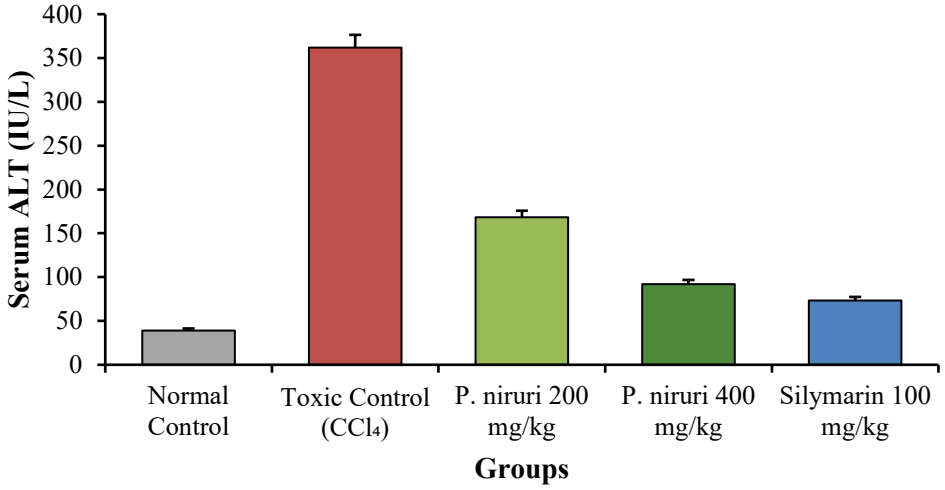


Figure 6.1: Effect of *Phyllanthus niruri* extract on serum ALT

The toxic control group exhibited a highly significant increase in the serum ALT ($p < 0.001$) from 39.03 IU/L of normal controls to 361.88 IU/L, which is a 9.3-fold increase and confirms hepatic injury was induced by CCl4 dosing. The increase is attributable to a CCl4-mediated lipid peroxidation of hepatocyte cell membrane, which is responsible for the leakage of the enzyme into the circulation.

Treatment with the extract at 200mg/kg and 400mg/kg respectively significantly reduced ($p<0.001$) serum ALT by 60.0% (168.32 IU/L) and 83.6% (92.00 IU/L) respectively when compared to toxic control. The protection was dose dependent, with the higher dose providing significantly greater protection than the lower ($p < 0.001$). ALT levels were significantly lowered at 100 mg/kg by Silymarin (73.32 IU/L, 89.4% protection) with no significant difference between the highest dose of Silymarin and the standard drug.

4.5. Effect on Hepatic Superoxide Dismutase (SOD)

The extract worked well to lower the amount of ALT leaking out from damaged cells, and the more of it was used, the more effective it was. This enzyme will open the protective enzymatic sequence, releasing super-oxid into peroxide of hydrogen and oxygen.

Table 4: Effect of Phyllanthus niruri Extract on Hepatic SOD in CCl_4-Induced Hepatotoxicity

Group	Treatment	SOD (U/mg protein)
I	Normal Control	13.19 ± 0.32
II	Toxic Control (CCl_4)	4.11 ± 0.29#
III	CCl_4 + P. niruri (200 mg/kg)	7.97 ± 0.30***
IV	CCl_4 + P. niruri (400 mg/kg)	11.07 ± 0.39***
V	CCl_4 + Silymarin (100 mg/kg)	11.31 ± 0.33***

*Mean ± SE, n = 6. #p < 0.05 versus normal control; ***p < 0.001 versus toxic control.*

The effect of CCl4 on hepatic SOD is represented in the table 6.9 which shows a decrease in SOD from 13.19 U/mg protein to 4.11 U/mg protein in the toxic control group as compared to the normal control group. The higher dose (400 mg/kg) restored activity to 7.97 U/mg protein ($p < 0.001$) which is similar to the activity of silymarin (11.31 U/mg protein); the lower dose (200 mg/kg) restored activity to 11.07 U/mg protein ($p < 0.001$).

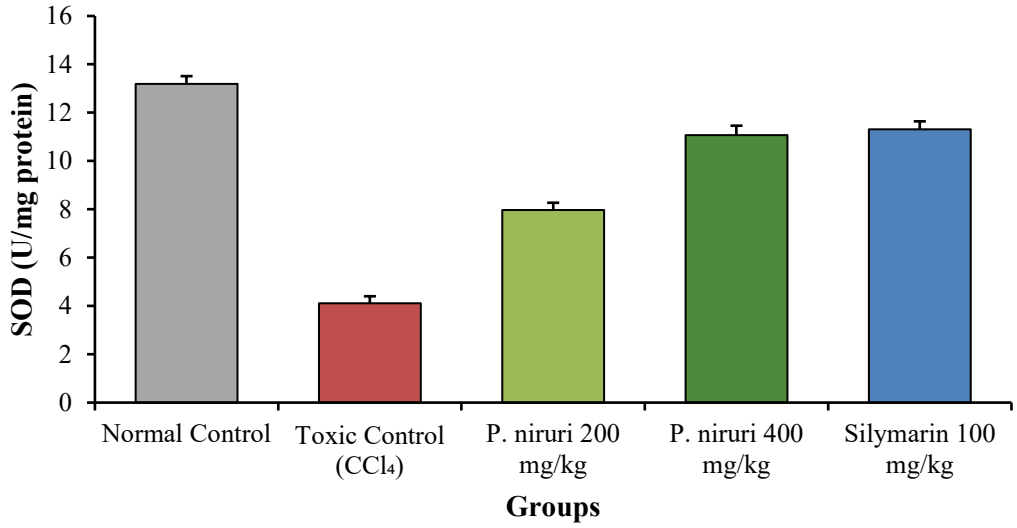


Figure 6.5: Effect of *Phyllanthus niruri* extract on hepatic SOD

Hepatic SOD decreased significantly ($p<0.001$) in the toxic group (4.11 U/mg protein) when compared with normal animals (13.19 U/mg protein), which shows a 68.8% decrease. Depletion of such an extent suggests that the enzyme is being used up at an excessive rate for scavenging the excess superoxide radicals produced during oxidant stress due to CCl4.

In comparison to the toxic control, which had SOD activity levels of 7.97 U/mg protein at 200 mg/kg and 11.07 U/mg protein at 400 mg/kg, respectively, the extract at both doses (200 and 400 mg/kg) significantly ($p < 0.001$) increased SOD activity in a dose-dependent manner, providing 42.5% and 76.6% protection, respectively. Similar result was obtained on silymarin (11.31 U/mg protein; 79.3% protection) and the highest dose of the extract was non statisentially different from the standard drug ($p>0.05$).

4.6. Histopathological findings

The semi-quantitative damage scores are listed in Table 5. Toxic control tissue was highly damaged (3.67 ± 0.21) while normal liver was not damaged (0.00). The extract lowered the score to 2.50 ± 0.22 at 200 mg/kg and 1.17 ± 0.17 at 400 mg/kg ($p < 0.001$), the latter matching silymarin (1.17 ± 0.17).

Table 5: Semi-Quantitative Scoring of Histopathological Changes in Liver

Parameter	Group I	Group II	Group III	Group IV	Group V
Overall hepatic damage score (0–4)	0.00 ± 0.00	3.67 ± 0.21#	2.50 ± 0.22***	1.17 ± 0.17***	1.17 ± 0.17***

*Mean ± SE, n = 6. Scale 0 (no damage) to 4 (severe damage). #p < 0.05 versus normal control; ***p < 0.001 versus toxic control.*

The hepatic cord was organised in a normal manner with the hepatocytes having distinct nuclei and granular cytoplasm, and unaltered sinusoids in the group I sections. Severe disruption of the group II sections was observed, accompanied by centrilobular necrosis, fatty degeneration, ballooned hepatocytes, inflammatory cell infiltration, dilated sinusoids and central vein congestion. Partial architectural restoration with moderate necrosis, fatty change and inflammatory infiltration were seen in Group III. In the Group IV, there was remarkable improvement with the cords of the liver arranged almost normally with mild fatty change, minimal inflammatory infiltration and regenerating hepatocytes. The organisation was almost normal in group V, hepatocytes were well preserved with little necrosis and inflammation.

5. CONCLUSION

This study demonstrates that Phyllanthus niruri hydroalcoholic whole plant extract significantly protects Wistar rats' livers against CCl_4 caused damage, and the effect is dose dependent. The extract exhibited an absence of mortality and apparent toxicity in its acute oral toxicity limit dose (2000 mg/kg), which improved the serum liver function markers, restored hepatic antioxidant activity, reduced lipid peroxidation and prevented body weight loss. The higher dose showed greater benefit and the hepatic damage score in the toxic control group was significantly decreased from 3.67 to 1.17, with some assessments similar to silymarin. These results suggest that P. niruri's antioxidant, membrane-protective, and anti-inflammatory characteristics are responsible for its hepatoprotective action. However, the outcomes are restricted to the experimental animal model and haven't been proven to be clinically effective or safe in human beings. Additional investigations should be carried out to determine the active phytoconstituents, to clarify the mechanism of action and to further assess the extract by conducting more preclinical studies before the therapeutic use can be considered.

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