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Research

Assessment of Nephroprotective Activity of Piper betle Herbal Extract in Paracetamol-Induced Kidney Toxicity in Rats

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Abstract:

The present study was designed to evaluate the nephroprotective activity of ethanolic extract of Piper betle against paracetamol-induced nephrotoxicity in rats. Nephrotoxicity was induced by administration of paracetamol, and the protective effect of the extract was assessed using biochemical, antioxidant, and histopathological parameters. Treatment with *Piper betle* extract significantly reduced serum creatinine, blood urea nitrogen, and uric acid levels compared to the toxic control group. Antioxidant enzyme levels including superoxide dismutase, catalase, and glutathione were significantly restored, while malondialdehyde levels were reduced. Histopathological examination revealed improvement in renal architecture with reduced tubular degeneration and inflammatory infiltration. The nephroprotective activity of *Piper betle* may be attributed to the presence of phenolic compounds and flavonoids possessing antioxidant and anti-inflammatory properties. The findings suggest that *Piper betle* could serve as a promising herbal therapeutic agent against drug-induced nephrotoxicity.

Keywords: Nephrotoxicity, Piper betle, Paracetamol, Oxidative stress

Introduction:

The kidneys are vital organs responsible for maintenance of fluid and electrolyte balance, excretion of metabolic waste products, and regulation of blood pressure and acid-base balance. Because of high blood flow and active metabolic functions, kidneys are highly susceptible to toxic injury caused by drugs and xenobiotics [1].

Drug-induced nephrotoxicity is a major clinical problem associated with several therapeutic agents including aminoglycosides, cisplatin, NSAIDs, and paracetamol [2]. Paracetamol is a widely used analgesic and antipyretic drug that causes severe hepatic and renal toxicity at toxic doses [3]. Toxicity is primarily mediated through the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), which induces oxidative stress, glutathione depletion, inflammation, and tubular necrosis [4].

Oxidative stress is considered one of the major mechanisms involved in renal injury. Excessive production of reactive oxygen species causes lipid peroxidation, mitochondrial dysfunction, and cellular necrosis [5]. Antioxidants capable of scavenging free radicals may therefore provide significant nephroprotection.

Medicinal plants have gained considerable attention as safer therapeutic alternatives because of their antioxidant and anti-inflammatory phytoconstituents [6]. Piper betle, commonly known as betel leaf, is a medicinal plant belonging to the family Piperaceae and has been traditionally used for treatment of inflammation, infections, and wounds [7].

The plant contains several bioactive compounds including hydroxychavicol, eugenol, flavonoids, tannins, and phenolic constituents possessing strong antioxidant activity [8]. Previous studies have demonstrated antimicrobial, hepatoprotective, antidiabetic, and cytoprotective properties of *Piper betle* extracts [9]. However, limited studies are

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available regarding its nephroprotective activity against paracetamol-induced kidney injury.

Therefore, the present study was undertaken to evaluate the nephroprotective effect of ethanolic extract of *Piper betle* against paracetamol-induced renal toxicity in rats.

Materials and Methods

Collection and Authentication of Plant Material

Fresh leaves of Piper betle were collected from the local market and authenticated by a qualified botanist. The leaves were washed thoroughly, shade dried, and powdered using a mechanical grinder.

Preparation of Extract

The powdered plant material was extracted using ethanol by Soxhlet extraction method. The extract was concentrated under reduced pressure using a rotary evaporator and stored in an airtight container for further studies.

Experimental Animals

Healthy Wistar albino rats weighing 150–200 g were used for the study. Animals were maintained under standard laboratory conditions with free access to food and water. Experimental procedures were conducted according to CPCSEA guidelines.

Acute Toxicity Study

Acute oral toxicity study was performed according to OECD guideline 423. The extract was found safe up to 2000 mg/kg body weight.

Experimental Design

Animals were divided into five groups containing six rats each:

Group	Treatment
Group I	Normal control
Group II	Paracetamol control
Group III	Standard treatment
Group IV	*Piper betle* extract (200 mg/kg)
Group V	*Piper betle* extract (400 mg/kg)

Paracetamol was administered to induce nephrotoxicity. The extract and standard drug were administered orally for the experimental period.

Biochemical Estimation

Blood samples were collected by retro-orbital puncture. Serum was separated and analyzed for serum creatinine, blood urea nitrogen, and uric acid using standard diagnostic kits.

Estimation of Antioxidant Parameters

Kidney homogenates were prepared for estimation of antioxidant parameters including superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), and malondialdehyde (MDA).

Histopathological Evaluation

Kidney tissues were fixed in 10% formalin, processed, embedded in paraffin wax, sectioned, and stained using hematoxylin and eosin for histopathological examination.

Statistical Analysis

Results were expressed as mean ± SEM. Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. Values of $p < 0.05$ were considered statistically significant.

Results

Paracetamol administration produced significant renal toxicity characterized by elevated serum creatinine, blood urea nitrogen, and uric acid levels compared to the normal control group. Treatment with ethanolic extract of Piper betle significantly reduced these elevated renal biomarkers in a dose-dependent manner.

The extract also restored antioxidant enzyme levels including SOD, CAT, and GSH while significantly reducing malondialdehyde levels, indicating inhibition of lipid peroxidation and oxidative stress.

Effect on Renal Biomarkers

Parameter	Normal Control	Toxic Control	Extract 200 mg/kg	Extract 400 mg/kg
Serum Creatinine (mg/dL)	0.68 ± 0.04	2.12 ± 0.08	1.31 ± 0.05	0.89 ± 0.04
Blood Urea Nitrogen (mg/dL)	18.2 ± 1.1	49.6 ± 2.3	31.5 ± 1.8	22.4 ± 1.2
Uric Acid (mg/dL)	2.8 ± 0.2	7.1 ± 0.4	4.9 ± 0.3	3.4 ± 0.2

Effect on Antioxidant Parameters

Parameter	Normal Control	Toxic Control	Extract 200 mg/kg	Extract 400 mg/kg
SOD (U/mg protein)	12.5 ± 0.6	5.1 ± 0.4	8.7 ± 0.5	11.2 ± 0.4
Catalase (U/mg protein)	54.3 ± 2.1	24.8 ± 1.6	39.5 ± 1.8	49.6 ± 2.0

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GSH (µmol/g tissue)	8.2 ± 0.4	3.1 ± 0.2	5.9 ± 0.3	7.4 ± 0.4
MDA (nmol/mg protein)	2.1 ± 0.1	6.8 ± 0.3	4.2 ± 0.2	2.9 ± 0.1

Histopathological examination of kidneys from toxic control animals revealed tubular degeneration, necrosis, and inflammatory infiltration, whereas treatment with *Piper betle* extract showed marked improvement in renal architecture.

Discussion

The present study demonstrated significant nephroprotective activity of ethanolic extract of Piper betle against paracetamol-induced renal toxicity in rats. Paracetamol administration caused marked elevation of renal biomarkers and oxidative stress parameters, confirming successful induction of nephrotoxicity.

Treatment with *Piper betle* extract significantly restored serum creatinine, blood urea nitrogen, and antioxidant enzyme levels. The reduction in malondialdehyde levels indicates inhibition of lipid peroxidation and oxidative stress-mediated renal injury.

The nephroprotective effect observed may be attributed to the presence of phenolic compounds, hydroxychavicol, flavonoids, and eugenol possessing potent antioxidant and anti-inflammatory properties. These phytoconstituents effectively scavenge reactive oxygen species and stabilize cellular membranes, thereby preventing tubular degeneration and renal damage.

Histopathological findings further confirmed the protective effect of the extract by demonstrating restoration of normal renal architecture and reduced inflammatory changes.

Conclusion

The present investigation concluded that ethanolic extract of Piper betle possesses significant nephroprotective activity against paracetamol-induced kidney toxicity in rats. The extract effectively improved renal function markers, restored antioxidant status, and reduced histopathological alterations.

The protective effect may be associated with antioxidant and anti-inflammatory phytoconstituents present in *Piper betle*. The findings support the traditional medicinal use of the plant and suggest its potential therapeutic application in management of drug-induced nephrotoxicity.

Further studies are required to isolate active constituents and investigate detailed molecular mechanisms responsible for nephroprotective activity.

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