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Effect of hydroalcoholic *Plectranthus vettiveroides* in glycerol-induced acute renal failure in rats

***Dr. Kavitha Rajesh, [1]Kannan Raman, [2]G. Gnana Jebaslin**

**Coordinator Department of Wellness, Faculty of Health Sciences, Male', Maldives National University.*
[1]Research Scholar, Department of Pharmaceutical Chemistry, JSS College of Pharmacy, Ooty, India
[2]Department of Pharmacology, Sree Krishna college of Pharmacy and Research centre,Parasala, Trivandrum, India.

Corresponding author: Dr. Kavitha Rajesh
Email: akil.kavi@gmail.com

ABSTRACT

The goal of this study was to see if hydroalcoholic extract of leaves of Plectranthus vettiveroides(HEPV) might help rats with glycerol-induced acute renal failure (ARF). The rats were given a single intramuscular injection of hypertonic glycerol (50 percent v/v; 8 ml/kg) to induce rhabdomyolytic ARF, and the animals were euthanized after 24 hours. The degree of renal damage was determined using plasma creatinine, blood urea nitrogen, creatinine clearance, and histological investigations. In a dose-dependent manner, pre-treatment with HEPV (125 and 250 mg/kg p.o. twice daily for 3 days) substantially reduced hypertonic glycerol-induced renal impairment. To investigate the mechanism of HEPV's renoprotective effects, researchers used BADGE (Bisphenol-A-diglycidyl ether) (30 mg/kg), a PPAR antagonist, and N(omega)-nitro-l-arginine-methyl ester (L-NAME) (10, 20, and 40 mg/kg), a nitric oxide synthase inhibitor. The therapeutic effects of HEPV in glycerol-induced renal impairment were reversed when BADGE (30 mg/kg) and L-NAME (40 mg/kg) were given. The hydroalcoholic extract of Plectranthus vettiveroides leaves has the ability to reduce myoglobinuric renal failure, and its renoprotective actions are mediated via activation of the PPAR and nitric oxide-dependent signalling pathways.

Keywords:*Plectranthus vettiveroides*, ARF, (PPAR)-γ, BADGE

INTRODUCTION

Acute renal failure (ARF) is defined by a fast dropin glomerular filtration rate (GFR) over a period of hours to days. Despite the use of numerous pharmacologic medications, the death rate of individuals with ARF is relatively high (25-70 percent). [1] Glycerol is used to induce ARF in animals. The most popular animal model of myoglobinuric ARF is intramuscular infusion of hypertonic glycerol, which causes a significant decrease in renal blood flow and GFR. [2] The acute volume depletion models of glycerol-induced ARF are said to be more closely comparable to the human ARF syndrome than the chronic dehydration model.

Rhabdomyolysis is one of the most common causes of ARF, with roughly 33% of rhabdomyolytic patients developing severe ARF. Rhabdomyolysis is a potentially fatal condition caused by the breakdown of skeletal muscle, which results in the release of intracellular contents into the circulatory system. Hypovolemia, acidosis, tubular obstruction, and the nephrotoxic effects of myoglobin are all known to contribute to rhabdomyolysis-induced ARF. [3]

Plectranthus vettiveroides **is** also known as *Coleus vettiveroides*, *Coleus zeylanicus*, *Plectranthuszeynanicus* (Lamiaceae). The main phytochemical components of Iris are diterpenoids, essential oils and phenols. About 140 diterpenes were identified from the coloured leaf glands of Platycladus species. The main components of Jerusalem artichoke essential oil are mono and sesquiterpenes. Flavonoids seem to be rare in *Platycladusorientalis*, only two flavonoids have been identified, 4',7-dimethoxy-5,6-cone in *Platycladusorientalis*, thus obtaining viologen from *P.marruboides* and golden chicken essence. Traditionally, it has been used as an antibacterial, deodorant, and cooling agent. It has also been used to prevent headaches and fever from burning eyes. The purpose of this research is to study the antibacterial activity of the stem bark of Phoenix tail. [4-8]

The nuclear receptor superfamily's peroxisome proliferator-activated receptors (PPARs) are divided into three isoforms, each encoded by a different gene: PPAR-, PPAR-/, and PPAR-. PPARs are ligand-dependent transcription factors that bind to particular peroxisome proliferator response elements (PPREs) at enhancer sites of regulated genes to control target gene expression. The glomerulus, collecting ducts, proximal tubules, and renal microvasculature have all been found to have PPAR-receptors. There have been reports suggesting that activation of PPAR-γ triggers protection in different models of renal failure like chronic renal allograft damage [9] and renal ischemia-reperfusion injury. [10] The studies have suggested that activation of PPAR-γ receptors directly attenuate glomerular diseases, possibly by inhibiting mesangial growth, which occurs early in the process of nephropathy. Furthermore, in glycerol-induced renal failure model, the generation of oxidative stress and proinflammatory mediators is reported to downregulate PPAR-γ expression. [11] The studies have shown that the extract of *P. vettiveroides*activates the PPAR-γ receptors [12] and therefore, the plant extract has been successfully used to treat type II diabetes mellitus, [13] to inhibit postprandial hyperglycaemia, and to diminish cardiac fibrosis. [14]

Nitric oxide (NO), a relaxing agent generated from the endothelium, is an important regulator of systemic and renal hemodynamic because it is required for the maintenance of a state of baseline vasodilation. NO is produced when NO synthesis catalyses the conversion of L-arginine to L-citrulline (NOS). Neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS have all been cloned and described (eNOS). The three isoforms are differentially expressed throughout the kidney with eNOS expression in renal vascular endothelial cells; nNOS in epithelial cells of the macula densa and the principal cells of the collecting duct and iNOS in tubule epithelia, including the proximal tubule, thick ascending limb, and distal convoluted tubule. [15] The NO generated from the expression of the different NOS isoforms has been shown to play an important role in various physiological processes in the kidney, including salt and fluid reabsorption, renin secretion, and tubuloglo merular feedback. [16] The specific effect produced by NO may be related to the location of the particular isoforms. The protective role of NO in different models of renal failure has been documented, [17] including glycerol-induced renal failure. [9],[18] The studies have shown that extract of *P.vettiveroides* restores the shear stress-induced decreased eNOS expression and reverses the stress-induced proatherogenic effects. [19] It has also been shown to increase the eNOS expression in obese Zucker rats. [20] Therefore, the present study was designed to investigate the potential of hydroalcoholic extract of leaves of *P. vettiveroides* in glycerol-induced ARF and to explore the role of PPAR-γ and NO in *P. vettiveroides* mediated biological actions.

MATERIALS AND METHODS

Drugs and Chemicals

Glycerol (LobaChemist Pvt. Ltd., India), BADGE (Bisphenol-A-diglycidyl ether) (Sigma-Aldrich, St. Louis, U.S.A.), and N(omega)-nitro-l-arginine-methyl ester (L-NAME) (Caymann Chemicals, USA) were used in the present study. Creatinine diagnostic kit was purchased from Medsource Ozone Biomedicals Pvt. Ltd, Haryana, India. Blood urea nitrogen kit was purchased from Erba Diagnostics Mannheim, Germany. All the other chemicals and reagents were purchased from S.D Fine Chemical Ltd. Mumbai, India, and were of analar quality. L-NAME was dissolved in 0.14 M NaCl, while BADGE was suspended in 0.5% carboxymethyl cellulose (CMC). All drug solutions were freshly prepared.

Plant Identification and Collection

The plant was collected from Namakkal, Tamil Nadu, India in January 2021. The herbarium specimens of plants are stored in the Pharmacognosy Department. The plant was identified by Dr. G.V.S.

Murthy, co-director of the Indian Botanical Survey in the South Ring of Coimbatore TNAU campus, who identified the plant with information he obtained from the literature.

Extraction

The leaves of*P. vettiveroides* were dried in shade and ground to make a coarse powder. The powder was then extracted thrice with methanol-water mixture (3: 1) by stirring at room temperature for 1 hour each time. The extract was filtered and the collected solvent was completely removed at 50°C under reduced pressure. The yield of the extract was 15% (w/w) in terms of dried starting material.

Animals

Wistar rats of either sex weighing 200 ± 50 g were utilized for this work. Animals were housed in polypropylene cages and maintained under the standard laboratory environmental conditions; temperature 25 ± 2ºC, 12 h light: 12 h dark cycle and 50 ± 5% relative humidity with free access to food and water *ad libitum*.

Induction of Myoglobinuric Acute Renal Failure

After a 24-hour water deprivation phase, rats were given an intramuscular injection of glycerol dissolved in saline (50 percent v/v, 8 ml/kg) in a split dosage in both hind limbs. The urine was collected by putting the animals in metabolic cages [18],[21]. [18] The animals were euthanized with a strong dosage of anaesthetic (diethyl ether) 24 hours after the glycerol injection, and the blood was collected in centrifuged tubes covered with ethylenediaminetetraacetic acid (EDTA). Blood samples were centrifuged at 4000 rpm for 30 minutes to separate the plasma. The kidneys were removed through a midline incision and were stored in 10% formalin for the histological examination.

Biochemical Parameters

Plasma creatinine

The plasma creatinine levels were evaluated by diagnostic kit based on principle of Jaffe's Method.

Blood urea nitrogen

The blood urea nitrogen (BUN) levels were evaluated with the diagnostic kit based on principle of glutamate dehydrogenase-urease method.

Creatinine clearance

- The total urine was collected in a period of 24 hours and creatinine clearance was calculated by the formula
- Creatinine clearance = U*V*24*60ml/min/P
- U = Creatinine concentration in urine; V = Total urine volume collected in period of 24 hours; P = Creatinine concentration in plasma.

Renal Histopathology

After the animal was sacrificed, the right kidney was separated and cleaned in ice-cold saline. It was then embedded in paraffin and histopathologically examined after being fixed in a 10% neutral buffered formalin solution. Deparaffinized, hydrated, and stained with hematoxylin and eosin, five-micrometer thick slices were cut. The renal sections were inspected blindly for intact glomeruli, bleeding and rupture, and medullary tubular cell vacuolization.

Experimental Protocol

Twelve groups, each comprising six Wistar albino rats, were employed in the present study. The animals were allowed free access to food but deprived of drinking water for 24 hours before glycerol injection.

Group I: Normal control

Rats received equivalent volume of saline corresponding to hypertonic glycerol in group II. All the animals were sacrificed after 24 hours of receiving saline and plasma creatinine, BUN, and creatinine clearance were assayed along with histopathological examination.

Group II: Glycerol-treated (8 ml/kg)

The rats received an intramuscular injection of 8 ml/kg hypertonic glycerol (50% v/v) as divided doses in both the hind limbs. All the animals were sacrificed 24 hours after treatment and different parameters were assessed, as described in group I.

Group III and IV: HEPV (125 and 250 mg/kg) in glycerol-treated

Hydroalcoholic extract of *P. vettiveroides*(125 and 250 mg/kg p.o) was suspended in 0.5% CMC and was administered twice daily at an interval of 12 hours, starting two days before the induction of ARF by glycerol. On the third day, HEPV was administered 30 minutes prior to glycerol injection and after 12 hours, same dose of HEPV was administrated in rats without administration of hypertonic glycerol. All the animals were sacrificed 24 hours after glycerol treatment and different parameters were assessed, as described in group I.

Group V: HEPV (250 mg/kg) per se

HEPVwas suspended in 0.5% CMC and was administered twice daily at an interval of 12 hours for three days. All the animals were sacrificed 12 hours after the last injection of *P. vettiveroides* and different parameters were assessed, as described in group I.

Group VI: HEPV (250 mg/kg) and bisphenol-A-diglycidyl ether (30 mg/kg) in glycerol-treated

Rats received HEPV (250 mg/kg p.o.) and BADGE (30 mg/kg p.o.) twice daily at an interval of 12 hours, starting two days before the induction of ARF by glycerol. On the third day, HEPVand BADGE were administered 30 minutes prior to glycerol injection and after 12 hours, same doses of HEPV and BADGE were administered in rats without administration of glycerol. All the animals were sacrificed 24 hours after glycerol treatment and different parameters were assessed, as described in group I.

Group VII: Bisphenol-A-diglycidyl ether (30 mg/kg) per se

Rats received BADGE (30 mg/kg p.o.) twice daily at an interval of 12 hours for 3 days. All the animals were sacrificed 12 hours after the last administration of BADGE. Different parameters were assessed as described in group I.

Group VIII, IX, and X: HEPV (250 mg/kg) and N(omega)-nitro-l-arginine-methyl ester (10, 20, and 40 mg/kg) in glycerol-treated

Rats received HEPV (250 mg/kg p.o.) and L-NAME (10, 20, and 40 mg/kg i.p.) twice daily at an interval of 12 hours, starting two days before the induction of ARF by glycerol. On the third day, *P. vettiveroides*and L-NAME were administered 30 minutes prior to glycerol injection and after 12 hours, same doses of *P. vettiveroides*and L-NAME were administered in rats without administration of glycerol. All the animals were sacrificed after 24 hours and different parameters were assessed, as described in group I.

Group XI: N(omega)-nitro-l-arginine-methyl ester (40 mg/kg) per se

Rats received an intraperitoneal injection of L-NAME (40 mg/kg) twice daily at an interval of 12 hours for 3 days. All the animals were sacrificed 12 hours after the last L-NAME injection and different parameters were assessed, as described in group I.

Group XII: Carboxymethyl cellulose per se

0.5% CMC (1 ml/kg p.o.) was administered twice daily at an interval of 12 hours, starting two days before the induction of ARF by glycerol. On the third day, CMC was administered 30 minutes prior to glycerol injection and after 12 hours, same dose of CMC was administrated in rats without administration of hypertonic glycerol. All the animals were sacrificed 24 hours after glycerol treatment and different parameters were assessed, as described in group I.

STATISTICAL ANALYSIS

The data were presented as mean ± S.E.M. One-way analysis of variance (ANOVA) followed by Tukey's multiple range test was applied to calculate the statistical significance between different various groups. A value of $P0 < 0.05$ was considered to be statistically significant.

RESULTS

In comparison to equivalent saline-treated normal rats, a single intramuscular injection of glycerol (50 percent v/v, 8 ml/kg) in split dosage in both hind limbs resulted in a substantial increase in plasma creatinine levels after 24 hours in glycerol-treated rats. In a dose-dependent manner, pre-treatment with a hydroalcoholic extract of *P. vettiveroides* (125 and 250 mg/kg p.o.) considerably reduced the glycerol-induced rise in plasma creatinine level. Administration of BADGE (30 mg/kg p.o.) and L-NAME (40 mg/kg i.p.) abolished the attenuating effects of HEPV (250 mg/kg p.o.) on glycerol-induced increase in plasma creatinine levels. Per se administration of L-NAME (40 mg/kg i.p.) and BADGE (30 mg/kg p.o.) did not alter the plasma creatinine levels in normal rats in a significant manner. Administration of CMC (1 ml/kg p.o) did not modulate plasma creatinine levels in glycerol-treated rats [Table 1].

Table 1: Effect of HEPV on blood urea nitrogen levels, plasma creatinine levels, and creatinine clearance in glycerol-induced renal failure in rats.

Groups	Blood Urea nitrogen (mg/dl)	Plasma creatinine (mg/dl)	Creatinine clearance (ml/min)
Control	18.8±1.1	1.6±0.2	0.51±0.03
Glycerol treated	53.6±2.5[a]	6.0±0.5 [a]	0.06±0.01 [a]
HEPV (125 mg/kg) + Glycerol	25.6±1.9[b]	3.0±0.3 [b]	0.45±0.03 [b]
HEPV (250 mg/kg) + Glycerol	19.0±3.3 [b]	2.3±0.4 [b]	0.51±0.02 [b]
HEPV (250 mg/kg) per se	19.8±0.9	1.8±0.1	0.52±0.03

HEPV (250 mg/kg) + Glycerol + BADGE (30mg/kg) per se	53.5±3.0[c]	6.6±0.3 [c]	0.06±0.01 [c]
BADGE (30mg/kg) per se	22.0±1.5	2.0±0.2	0.52±0.04
HEPV (250 mg/kg) + Glycerol+ L-NAME (10mg/kg)	21.2±2.8	2.8±0.2	0.53±0.04
HEPV (250 mg/kg) + Glycerol+ L-NAME (20mg/kg)	23.6±2.9	3.1±0.1	0.55±0.00
HEPV (250 mg/kg) + Glycerol+ L-NAME (40mg/kg)	56.1±3.3 [c]	6.6±0.3 [c]	0.05±0.04 [c]
L-NAME (40mg/kg) per se	22.8±1.9	2.1±0.3	0.55±0.03
CMC + Glycerol	51.8±2.6	5.8±0.4	0.04±0.00

CMC: Carboxy mehyl cellulose. Values are expressed as mean ±S.E.M. for n=6 rats, where [a]P< 0.05 vs normal control; [b]P<0.05 vs glycerol treated; [c]P<0.05 vs HEPV (250mg/kg)

In comparison to equivalent saline-treated normal rats, a single intramuscular injection of glycerol (50 percent v/v, 8 ml/kg) in split dosage in both hind limbs resulted in a substantial increase in BUN levels after 24 hours in glycerol-treated rats. Pre-treatment with *P. vettiveroides* hydroalcoholic extract (125 and 250 mg/kg p.o.) significantly reduced the glycerol-induced increase in BUN levels. The attenuating effects of HEPV (250 mg/kg p.o.) on glycerol-induced increases in BUN levels were reduced when BADGE (30 mg/kg p.o.) and L-NAME (40 mg/kg i.p.) were given. Per se administration of L-NAME (40 mg/kg i.p.) and BADGE (30 mg/kg p.o.) did not alter the BUN levels in normal rats in a significant manner. Administration of CMC (1 ml/kg p.o.) did not modulate BUN levels in glycerol-treated rats [Table 1].

In comparison to equivalent saline-treated normal rats, a single dose of intramuscular glycerol (50 percent v/v, 8 ml/kg) in split dosage in both hind limbs resulted in a substantial reduction in creatinine clearance after 24 hours in glycerol-treated rats. Pre-treatment with P. vettiveroides hydroalcoholic extract (125 and 250 mg/kg p.o.) significantly decreased the glycerol-induced reduction in creatinine clearance. Administration of BADGE (30 mg/kg p.o.) and L-NAME (40 mg/kg i.p.) abolished the attenuating effects of *P. vettiveroides*(250 mg/kg) on glycerol-induced decrease in creatinine clearance. Per se administration of L-NAME (40 mg/kg i.p.) and BADGE (30 mg/kg p.o.) did not alter the creatinine clearance in normal rats in a significant manner. Administration of CMC (1 ml/kg p.o.) did not modulate creatinine clearance in glycerol-treated rats. [Table 1].

Renal Histopathology

Glycerol administration caused histological changes such as burst glomeruli, bleeding, and vacuolization of medullary tubular cells. Pre-treatment with HEPV (125 and 250 mg/kg) reduced the histopathological changes caused by glycerol [Figure 1]. The attenuating effects of HEPV (250 mg/kg) on glycerol-induced histopathological changes were reversed when BADGE (30 mg/kg p.o.) and L-NAME (40 mg/kg i.p.) were given.

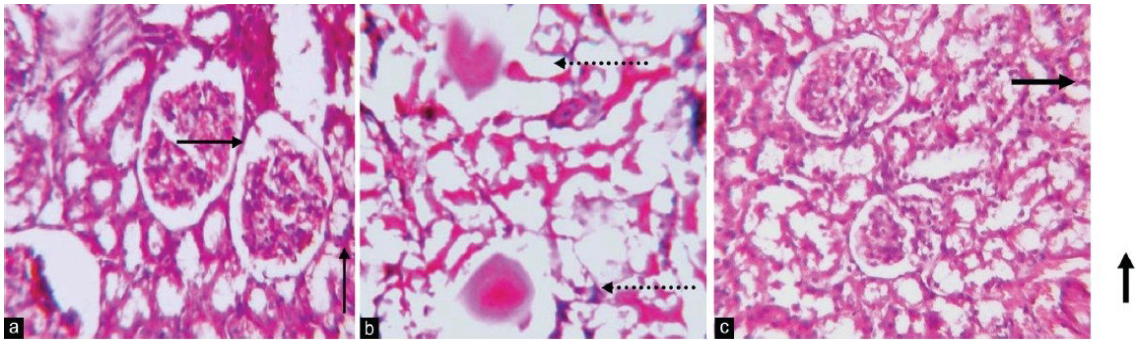

Figure 1: Hematoxylin and eosin-stained sections of rat kidneys in light microscopy (Original magnifi cation ×100): Kidney section of saline-treated rats, showing intact glomeruli represented by normal arrow in addition shows normal medullary tubular cells (a). Kidney section of glycerol-treated rats shows rupture glomeruli shown by broken arrow, also rupture and vacuolization of medullary tubular cells represented by broken arrow (b). Kidney section of rats pretreated with *P. vettiveroides*is shown by bold arrow, before glycerol shows almost near morphology to saline-treated normal rats (c)

DISCUSSION

In this investigation, a single intramuscular injection of hypertonic glycerol (8 ml/kg) in a split dosage in both hind limbs caused ARF within 24 hours, as measured by decreased creatinine clearance, increased plasma creatinine and BUN levels, and histological changes. One of the most often utilised animal models of ARF is glycerol-induced renal failure. [2],[21] Rhabdomyolysis, which leads to ARF, has been recorded after intramuscular injection of hypertonic glycerol. Rhabdomyolysis is a potentially life-threatening syndrome characterized by the breakdown of skeletal muscle, resulting in the subsequent release of intracellular contents from myocytes into the circulatory system. [3]

Pre-treatment with a hydroalcoholic extract of *P. vettiveroides* leaves (125 and 250 mg/kg p.o.) significantly reduced glycerol-induced renal impairment in the current study. In rats, the juice of *P. vettiveroides* has been shown to protect them from ethylene glycol-induced nephrolithiasis. [8] This is the first evidence that we are aware of that suggests the preventive benefits of a hydroalcoholic extract of *P. vettiveroides* leaves in rats with myoglobinuric ARF.To explore the possible mechanism of renoprotective effect of *P. vettiveroides*, BADGE, a PPAR-γ antagonist, was employed in the present investigation. [22] Administration of BADGE (30 mg/kg) significantly attenuated *P. vettiveroides*-mediated nephroprotective effects in glycerol-induced renal failure, suggesting that the noted beneficial effects of *P. vettiveroides* in the present study is mediated through activation of PPAR-γ receptors.

PPARs are transcription factors belonging to the nuclear receptor superfamily and are activated by fatty acids, eicosanoids, and various synthetic ligands. PPAR-γ isoform has been shown to control numerous physiological functions including glucose metabolism, adipocyte differentiation, lipid synthesis and its uptake. PPAR-γ agonists are presently employed clinically for the management of type II diabetes mellitus. It is becoming increasingly clear that PPAR-γ ligands represent a promising therapeutic strategy for other diseases as well, including atherosclerosis, cancer, cardiovascular complications, neuropathic pain, spinal cord injury, and neurodegenerative disorders such as Alzheimer's disease. [23]

The effect of PPAR- in modulating renal functioning has also been explored. Activation of PPAR- has been linked to protection in many models of renal failure, including chronic renal allograft damage [9] and renal ischemia-reperfusion injury. [10] Furthermore, it has been demonstrated that diminished PPAR-x expression and activity is implicated in the pathophysiology of glycerol-induced ARF, and that reversing renal damage using ciglitazone, a PPAR-x activator, is possible. [24] There have been a number of studies suggesting that methanolic extract of leaves of *P. vettiveroides*activates PPAR-γ receptors. [13] Furthermore, the beneficial effects of *P. vettiveroides*in improving insulin receptor sensitivity in Zucker diabetic fatty rats, [13] inhibiting postprandial hyperglycaemia and in diminishing cardiac fibrosis, [14] have been shown to be mediated through activation of PPAR-γ receptors.

There have been reports suggesting that ethanolic extract of leaves of *P. vettiveroides*modulate different functions through NO signalling pathway. [7] It has been reported that *P. vettiveroides* reverses shear stress-induced proatherogenic effects by increasing the eNOS expression. [19] Furthermore, it has also been documented to improve the arterial functions in obese Zucker rats by increasing eNOS expression. [20] Therefore, to investigate the contributory role of NO in *P. vettiveroides*-mediated renoprotection, L-NAME, NOS inhibitor, was employed in three-dose schedule, i.e., 10, 20, and 40 mg/kg. Administration of L-NAME (40 mg/kg i.p.) significantly attenuated *P. vettiveroides*-mediated renoprotection in glycerol-induced renal failure, suggesting the key role of NO in renoprotective effects of *P. vettiveroides*. Per se administration of L-NAME for 2 days (40 mg/kg) did not modulate renal functions in the normal rats. The protective role of NO in different models of renal failure has been documented, [17] including glycerol-induced renal failure. [18],[25] These studies have demonstrated that levels of NO are decreased in glycerol-induced renal failure and different agents have shown to produce renoprotection by increasing the NO production. In the present study, single dose of BADGE was employed, while L-NAME was administered at three-dose levels. The dose of BADGE (30 mg/kg) was selected on the basis of our own previous study, suggesting that the beneficial effect of curcumin in experimental dementia involves activation of PPAR-γ receptors. [22] However, for L-NAME, three doses with the range of 10, 20, and 40 mg/kg were used so as to select the proper dose and in the present study, 40 mg/kg was shown to attenuate the protective effects of *P. vettiveroides*.

Endothelial PPAR- controls vascular NO generation, according to new research. The Akt-eNOS signalling pathway has been related to enhance NO production driven by PPAR activation. [26] NO, on the other hand, has been demonstrated to activate PPAR- and enhance its PPRE binding (PPAR response element). [27],[28] These findings suggest that these two signalling channels are connected and form an integrated system that produces protective

benefits, including renoprotection, in rats with glycerol-induced ARF.

CONCLUSION

It may be concluded that hydroalcoholic extract of *P vettiveroides* leaves has ameliorative potential in reducing myoglobinuric renal failure, and that its renoprotective actions may be mediated through activation of the PPAR and NO-dependent signalling pathways.

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