Sinapic Acid Attenuates Cisplatin-induced Nephrotoxicity through Peroxisome Proliferator-activated Receptor Gamma Agonism in Rats

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Aim: The aim of this study was to investigate the involvement of peroxisome proliferator-activated receptor gamma (PPAR-γ) in renal protection offered by sinapic acid in cisplatin-induced nephrotoxicity in male rats. Materials and Methods: Nephrotoxicity was induced by single dose of cisplatin (5 mg/kg, intraperitoneal [i.p.]) in rats. Cisplatin-induced nephrotoxicity was assessed by measuring serum creatinine, creatinine clearance, urea, uric acid, potassium, magnesium levels, fractional excretion of sodium, and microproteinuria in rats. Superoxide anion generation, thiobarbituric acid reactive substances, myeloperoxidase activity, and reduced glutathione levels were measured to assess oxidative stress in renal tissues. Hematoxylin and eosin stain showed renal histological changes. Results: The significant changes in serum and urinary parameters, elevated oxidative stress, and renal histological changes established the induction of nephrotoxicity. Sinapic acid treatment (20 and 40 mg/kg, orally [p.o.]) provides dose-dependent and significant (P < 0.05) nephroprotection against cisplatin-mediated nephrotoxicity in rats. Nephroprotective effect of sinapic acid was abolished by PPAR-γ inhibitor, bisphenol A diglycidyl ether (30 mg/kg, i.p.) in rats. Conclusion: It is concluded that PPAR-γ agonism serves as one of the mechanisms in sinapic acid-mediated renoprotection.

Keywords: Bisphenol A diglycidyl ether, cisplatin, nephrotoxicity, oxidative stress, peroxisome proliferator-activated receptor-gamma, renoprotection, sinapic acid

INTRODUCTION

The kidneys are the primary organs responsible for the maintenance of extracellular fluid volume and homoeostasis. As a result of which, kidneys are exposed to harmful substances leading to the damage of renal tissues as well as degeneration of parenchymal cells.[1] Nephrotoxicity is one of the most widely recognized side effects related with malignancy chemotherapy in which the urine output reduces to less than half of the normal volume, whereas the level of serum creatinine and other nitrogenous and biochemical wastes is increased in body.[2,3]

Cisplatin is the most successful chemotherapeutic agent used in the treatment of solid tumor. Still, neurotoxicity, ototoxicity, nausea, vomiting, and especially nephrotoxicity are the main restraining factors for the use of cisplatin in treatment of cancer. Among these side effects, the predominance of nephrotoxicity is very high.[4] Cisplatin-induced nephrotoxicity affects nearly 20%–30% patients receiving therapeutic dose.[5] Moreover, the chance of nephrotoxicity increases significantly along with patient age and comorbidities.[6-8]

Several studies indicate that cisplatin accumulation in kidneys results in inflammation, increases lipid peroxidation, and reduces the level of antioxidant,
mitochondrial dysfunction, along with deoxyribonucleic acid (DNA) adduct formation and activation of apoptotic pathways.\[^9\] Moreover, the accumulation of cisplatin is found to be more than five times in kidney as compared to the blood. As a result of which, the concentration of cisplatin in kidney is very high (resulting in toxicity) as compared to the concentration in the blood which is generally nontoxic. This accumulation of cisplatin is responsible for the development of renal dysfunction and nephrotoxicity.\[^10-12\]

Plants are important source of photochemical, which are proven as effective therapeutic agents. Many phytoconstituents such as flavonoids and alkaloids isolated form plants are found to be effective drugs for various disorders. Moreover, several phenolic compounds present in food such as rosemary, oregano, ginger, green tea, and soybean have been found to be significantly effective antioxidant agents.\[^13\] The oxidative stress and apoptotic pathway is an important factor responsible for several diseases. Due to increasing involvement of oxidative stress in pathological conditions, antioxidants and antiapoptotic substances are considered as potential therapeutic agents.\[^14\]

Sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid) is a hydroxycinnamic acid of phenylpropanoid family that is abundantly present in plant kingdom such as spices, wheat, rice, oil seeds, vegetables, fruits especially citrus fruits, cereals, vinegar, and wine.\[^15\] Moreover, sinapic acid has become a major active component of Chinese traditional remedies.\[^16\] Sinapic acid is proved as an antimicrobial,\[^17\] neuroprotective,\[^18\] antihyperglycemic,\[^19\] anxiolytic,\[^20\] anti-inflammatory,\[^21\] peroxynitrite scavenging,\[^22\] antihypertensive, anticancer, and as an antioxidant agent.\[^23, 24\]

Researchers proved the involvement of nuclear receptor peroxisome proliferator-activated receptors (PPARs) especially PPAR-gamma (PPAR-\(\gamma\)) in the transcriptional modulation of diverse cellular functions such as lipid metabolism, inflammation, glucose homeostasis, cell differentiation, and extracellular matrix remodeling.\[^25\] Activated PPAR-\(\gamma\) pathway is proved as an important target in diabetes, obesity, atherosclerosis, hypertension, cancer chemoprevention, and drug-induced nephropathy.\[^26, 27\] PPAR-\(\gamma\)-expression in glomerulus, medullary thick ascending limb, proximal tubules, and collecting ducts of kidney imparts a significant role in renal metabolism and maintenance of systemic homeostasis.\[^28\] Moreover, PPAR-\(\gamma\)-attenuated glomerulonephritis acts on macrophages to produce anti-inflammatory effects as well as improve the metabolic parameters in type-2 diabetes.\[^29\] PPAR-\(\gamma\) agonists were also reported to possess nephroprotective effects in different animal models via anti-inflammatory, antioxidant, vascular, metabolic, and hemodynamic effects.\[^30\] Several antioxidant and anti-inflammatory natural products are also found to activate peroxisome PPARs; therefore, these compounds may help to overcome drug-induced cytotoxicity by modulating PPAR-\(\gamma\) transduction pathway.\[^31-33\]

In preview of previous studies, this study was framed to investigate the protective effect of sinapic acid against cisplatin-induced nephrotoxicity in rats, as well as to explore the role of PPAR-\(\gamma\) in nephroprotection.

Materials and Methods

The study was executed as per the instructions of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment, Forests and Climate Change, Government of India. In this study, inbred male Wistar albino rats weighing 200–250 g were used.\[^34\] The rats were kept on standard rat diet and water \textit{ad libitum} while exposing to 12-h light and dark cycles. At the end of study, blood samples were withdrawn to measure parameters. After that animals were euthanized under the influence of anesthesia and kidneys were harvested.

Drugs and chemicals

Sinapic acid, cisplatin, bisphenol A diglycidyl ether (BADGE), and other chemicals were obtained from Sigma-Aldrich, Bangalore, India. All other agents used were of analytical grade.

Induction of nephrotoxicity

Animals were divided into five groups and each group comprised six rats. Nephrotoxicity was induced by intraperitoneal single dose of cisplatin (5 mg/kg) on the first day of study. Sinapic acid was dissolved in 0.2% dimethyl sulfoxide (DMSO) and was administered at two dose levels (20 and 40 mg/kg, orally \{p.o.\}) to rats for 5 days. BADGE was dissolved in minimal volume of ethanol and final volume was made with 0.9% saline. After 4 days, the rats were kept individually in metabolic cages for the next 24 h. On the fifth day, rats were removed from metabolic cages; their blood samples were collected and euthanized by cervical dislocation under anesthesia. Serum creatinine, urea, uric acid, magnesium, and potassium levels were estimated in blood samples. The microprotein, sodium, and creatinine levels were also determined in urine samples. A part of renal tissue was fixed with formalin for histopathological studies and a small portion of renal tissue was used for estimation of superoxide anion generation (SAG). The remaining of renal tissue was used to estimate myeloperoxidase (MPO), hydroxyproline, thiobarbituric acid reactive substances
(TBARS), reduced glutathione (GSH) levels, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β).\textsuperscript{[35-44]}

**Experimental protocol**

The animals were divided into different groups and each group comprised of six animals.

*Group 1 (vehicle control)*: Vehicle (saline, 10 mL/kg, intraperitoneal [i.p.]) for cisplatin was administered on day 1 only. Vehicle (0.2% DMSO in water, 10 mL/kg, p.o.) for sinapic acid was administered once daily for 4 days to the male Wistar rats.

*Group 2 (disease control)*: The nephrotoxicity was induced by single dose of cisplatin (5 mg/kg, i.p.) on day 1 to the male Wistar rats.

*Group 3 (sinapic acid (20 mg/kg) + cisplatin group)*: Sinapic acid (20 mg/kg/day, p.o.) was administered to experimental animals for 4 days after administration of single dose of cisplatin (5 mg/kg, i.p.) on day 1.

*Group 4 (sinapic acid (40 mg/kg) + cisplatin group)*: Sinapic acid (40 mg/kg/day) was administered to experimental animals for 4 days after administration of single dose of cisplatin (5 mg/kg, i.p.) on day 1.

*Group 5 (sinapic acid (40 mg/kg) + BADGE (30 mg/kg) group)*: BADGE (30 mg/kg, i.p.) was administered 30 min before treatment of animals with 40 mg/kg/day sinapic acid for consequent 4 days after administration of single dose of cisplatin (5 mg/kg, i.p.) on day 1.

**Statistical analysis**

Results were expressed as mean ± standard error of mean. The data obtained from various groups were statistically analyzed using one-way analysis of variance followed by Tukey’s multiple range tests. The value of *P* < 0.05 was considered to be statistically significant.

**RESULTS**

No significant change was observed in different renal and oxidative parameters in the case of vehicle control group.

**Effect of sinapic acid treatment on serum creatinine, creatinine clearance, serum urea, uric acid, and serum potassium and magnesium level**

A significant decrease was observed in creatinine clearance level in urine, serum potassium, and serum magnesium levels, whereas serum creatinine, serum urea, and uric acid levels were found to be increased significantly (*P* < 0.05) in cisplatin (5 mg/kg, i.p.) group as compared to vehicle control group. The treatment with sinapic acid (20 and 40 mg/kg, p.o.) significantly and dose dependently (*P* < 0.05) increased creatinine clearance rate, serum potassium, and serum magnesium level, whereas it decreased the elevated level of serum creatinine and serum urea, as well as uric acid levels as compared to cisplatin group. The prior treatment with BADGE (30 mg/kg, i.p.) significantly (*P* < 0.05) abolished the renoprotective effect offered by sinapic acid [Table 1].

**Effect of sinapic acid treatment on fractional excretion of sodium and microprotein urea**

A significant (*P* < 0.05) increase in fractional excretion of sodium (FeNa) level in serum and microprotein urea level in urine was noticed in the cisplatin group (5 mg/kg, i.p.) as compared with the vehicle control group. Treatment with sinapic acid (20 and 40 mg/kg, p.o.) produced a significant decrease in FeNa and microproteinuria as compared to cisplatin control group. Pretreatment with BADGE (30 mg/kg, i.p.) considerably attenuated the protection produced by sinapic acid [Table 1].

**Effect of sinapic acid treatment on hydroxyproline thiothobarbituric acid reactive substances, renal superoxide anion generation, myeloperoxidase, and glutathione levels**

The level of hydroxyproline, renal TBARS, SAG, and MPO activity was found to increase in cisplatin group (5 mg/kg, i.p.), whereas GSH level decreased as compared with the vehicle control group [Figure 1 and Table 2]. Administration of sinapic acid (20 and 40 mg/kg, p.o.) dose dependently produced a significant (*P* < 0.05) reduction in the hydroxyproline [Figure 1]. Moreover, sinapic acid attenuated cisplatin-induced rise in renal TBARS, SAG, and MPO activity along with raising the renal GSH levels in rats [Table 2]. Pretreatment with BADGE abolished sinapic acid-mediated correction of renal parameters in rats.

**Effect of sinapic acid treatment on pro-inflammatory cytokine levels**

TNF-α and IL-1β level were found to be significantly (*P* < 0.05) elevated in the cisplatin group (5 mg/kg, i.p.) as compared to vehicle control group indicating inflammation. Administration of sinapic acid dose (20 and 40 mg/kg, p.o.) dose dependently and significantly (*P* < 0.05) attenuated the elevated levels of TNF-α and IL-1β as compared to cisplatin control group [Figures 2 and 3].

**Effect of sinapic acid treatment on histopathological evaluation**

Histopathological examination of renal tissue from normal rat showed normal structure of the glomeruli and tubules (A). Cisplatin control rats showed coagulative necrosis and severe degenerative changes in the tubular...
Singh, et al.: PPAR-γ and sinapic acid lining (B). Administration of sinapic acid (20 and 40 mg/kg, p.o.) resulted in a significant improvement of the overall histopathological picture of the kidneys. The renal tissues of vehicle control group rats stained with hematoxylin and eosin show intact glomerulus surrounded by medulla Bowman capsule, convoluted tubules, loop of Henle, and collecting tubule. The cisplatin control group showed distorted histology such as atrophied glomerulus, collecting tubules showing necrosis, vacuolization, neutrophil accumulation, and loss of normal architecture. Administration of sinapic acid produced significant protection by attenuating the inflammation, vacuolization, and necrosis (C). Treatment with BADGE attenuated the protection provided by sinapic acid against cisplatin-induced nephrotoxicity in rodents (D) [Figure 4].

**DISCUSSION**

The duration and dose-related nephrotoxicity is the main side effect of cisplatin, which confines its clinical use as a chemotherapeutic agent.13 Slow excretion rate and high accumulation of cisplatin in kidney as compared...
Singh, et al.: PPAR-γ and sinapic acid to blood are the main factors responsible for cisplatin-induced deleterious effects.\textsuperscript{[43]} Cisplatin-induced oxidative stress in renal tissue causes inflammation that produces structural damages, renal dysfunction, and apoptosis, which lead to nephrotoxicity.\textsuperscript{[46]} Cisplatin-induced nephrotoxicity was found to be associated by altered level of MPO, hydroxyproline, TBARS, SAG, and GSH. Several previous studies clearly indicated the role of free radical formation and oxidative stress in cisplatin-induced nephrotoxicity.\textsuperscript{[47-49]} Similarly, in this study, levels of MPO, hydroxyproline, and TBARS were found to be elevated, whereas levels of antioxidant enzymes were found to be reduced as compared to normal rats. In this study, the treatment with sinapic acid (20 and 40 mg/kg, p.o.) significantly attenuated the cisplatin-induced altered renal marker levels and increased oxidative stress. These outcomes were in accordance with those obtained in previous studies, which showed that antioxidative potential of sinapic acid has protective activity against cisplatin-induced nephrotoxicity.\textsuperscript{[50-54]}

The cisplatin-induced altered renal marker levels and oxidative stress parameters in rats

| Parameter          | Vehicle control | Cisplatin control (5 mg/kg, i.p.) | Cisplatin + sinapic acid (20 mg/kg, p.o.) | Cisplatin + sinapic acid 40 mg | Cisplatin + sinapic acid 40 mg + BADGE |
|--------------------|----------------|----------------------------------|------------------------------------------|-------------------------------|----------------------------------------|
| TBARS (µM/mg of protein) | 0.45 ± 0.04 | 1.55 ± 0.05\textsuperscript{a} | 0.75 ± 0.04\textsuperscript{b} | 0.58 ± 0.03\textsuperscript{b} | 1.28 ± 0.07\textsuperscript{c} |
| SAG (µM/mg of tissue) | 21.4 ± 0.64 | 65.2 ± 1.39\textsuperscript{a} | 45.1 ± 1.24\textsuperscript{b} | 35.2 ± 0.86\textsuperscript{b} | 62.8 ± 1.38\textsuperscript{c} |
| MPO (U/g of tissue)  | 1.79 ± 0.52 | 6.91 ± 0.91\textsuperscript{a} | 5.02 ± 2.31\textsuperscript{b} | 2.06 ± 0.63\textsuperscript{b} | 5.24 ± 0.96\textsuperscript{c} |
| GSH (mM/mg of protein) | 16.2 ± 0.41 | 5.35 ± 0.52\textsuperscript{a} | 12.65 ± 0.52\textsuperscript{b} | 14.18 ± 0.33\textsuperscript{b} | 7.82 ± 0.64\textsuperscript{c} |

TBARS = thiobarbituric acid reactive substances, SAG = superoxide anion generation, MPO = myeloperoxidase, GSH = glutathione, BADGE = bisphenol A diglycidyl ether, i.p. = intraperitoneal, p.o. = orally

Data were expressed as mean ± standard error of mean (n = 6)

\textsuperscript{a}P < 0.05 versus vehicle control group

\textsuperscript{b}P < 0.05 versus cisplatin (5 mg/kg, i.p.)

\textsuperscript{c}P < 0.05 versus cisplatin + sinapic acid (40 mg/kg, p.o.)

Figure 2: Effect of various treatments on level of tumor necrosis factor-alpha (TNF-α) in renal tissue. Data were expressed as mean ± standard error of mean (n = 6). \textsuperscript{a}P < 0.05 versus vehicle control group; \textsuperscript{b}P < 0.05 versus cisplatin (5 mg/kg, intraperitoneal [i.p.]); \textsuperscript{c}P < 0.05 versus cisplatin + sinapic acid (40 mg/kg, orally [p.o.])
responses. In inflamed renal parenchyma the IL-1β promotes the influx of circulating monocytes, whereas TNF-α enhances the level of leucocytes in the inflamed renal parenchyma in renal endothelial cells. In a study by Ansari, inflammatory cytokine levels (TNF-α and IL-1β) were found to reduce by administration of sinapic acid. In this study, a well-established anti-inflammatory agent, sinapic acid pretreatment (40 mg/kg), significantly downregulated TNF-α and IL-1β levels by averting the inflammatory infiltration and apoptosis of renal tubules in cisplatin nephrotoxicity. Histopathological examination shown that sinapic acid treatment decreased the neutrophil infiltration and glomerular atrophy, and restored the texture of in renal tissue. We can summarize that the sinapic acid can produce nephroprotective effect by abolishing renal dysfunctioning, oxidative stress, and increased free radicals produced by cisplatin.

The nuclear receptor, PPAR-γ, is mainly involved in storage of fat and controls the metabolism, inflammation in immune cells, and cell proliferation. Substances that are PPAR-γ agonists also show anti-inflammatory, antidiabetic, antifibrotic, antioxidant, and antiapoptotic effects and protective effects against renal ischemia/reperfusion. Early reports also documented that due to expression of PPAR-γ in renal tissues such as renal microvasculature, glomerulus, proximal, and collecting tubules produce beneficial role in renal disorders by regulation inflammatory mediators into renal tissues, inhibiting the intracellular cell adhesion molecule-1 expression and consequently reducing the oxidative stress level. Downregulation of PPAR-γ, TNF-α level, and elevation of IL are the indicators of inflammation and elevation of oxidative stress. It was also documented that renal expression of PPAR-γ was reduced by cisplatin, whereas Hwang et al. reported that sinapic acid could protect the differentiation potential of stem cells against ultraviolet-A irradiation by upregulation of PPAR-γ. It was also reported that administration of BADGE, a PPAR-γ inhibitor, abolished the antioxidant effect of PPAR-γ agonist, confirming the PPAR-γ mediated protective role of in antioxidant against cisplatin-induced nephrotoxicity. In this study, dose-dependent renoprotective effect of PPAR-γ agonist, sinapic acid, was abolished by BADGE as supported by the histopathological findings.

Hence, as per above discussion, it is can be summarized that the sinapic acid can produce nephroprotective effect in the case of nephrotoxicity caused by cisplatin. Moreover PPAR-γ activation imparts an important role in sinapic acid-mediated nephroprotection against cisplatin-induced nephrotoxicity.
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Conflicts of interest

There are no conflicts of interest.

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