

Severe Acute Kidney Injury Associated with a Corosolic Acid-Containing Supplement: A Case Report with In Vitro Evidence of Proximal Tubular Toxicity

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Received: 02 Oct 2026

Accepted: 12 Oct 2026

Published: 14 Oct 2026

J Short Name: ACMCR

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Citation:

Sun-Hee Park, Severe Acute Kidney Injury Associated with a Corosolic Acid-Containing Supplement: A Case Report with In Vitro Evidence of Proximal Tubular Toxicity. Ann Clin Med Case Rep® 2026; V17(1): 1-7

Keywords:

Acute Kidney Injury; Corosolic Acid; Dietary Supplement; Ferroptosis; Proximal Tubular Injury

1. Abstract

1.1. Background

Corosolic acid is a Banaba-derived pentacyclic triterpenoid marketed for glycemic control, but its renal safety remains poorly characterized.

1.2. Case Presentation

A 66-year-old man with type 2 diabetes mellitus and hypertension presented with nausea, vomiting, poor oral intake, and watery diarrhea after taking a corosolic acid-containing supplement for 15 days. He had continued taking the supplement until the morning of admission, when it was discontinued. His renal function had been normal 5 months earlier. On admission, blood urea nitrogen and serum creatinine levels were 101 and 14.6 mg/dL, respectively, and he had oliguria, hyperkalemia, and metabolic acidosis. He required four hemodialysis sessions, and his renal function recovered progressively after discontinuation of the supplement and supportive care.

In vitro findings: In experiments using HK-2 proximal tubular epithelial cells, corosolic acid reduced cell viability at 8 μ M and caused marked cytotoxicity at concentrations of 10 μ M or higher. Corosolic acid also increased mRNA expression of LCN2, NOX4, HMOX1, HMGB1, and SOD2, decreased catalase mRNA expression, and induced a dose- and time-dependent depletion of GPX4 protein without a pro-apoptotic increase in the BAX/BCL2 ratio.

1.3. Conclusion

The temporal association, the clinical dechallenge, and the proximal tubular toxicity observed in vitro support a possible nephrotoxic contribution of corosolic acid. Volume depletion and concomitant medications are likely to have acted as important

cofactors. These findings raise concern about the use of corosolic acid-containing supplements during acute illness or volume depletion.

2. Introduction

Corosolic acid, also known as 2 α -hydroxy-ursolic acid, is an ursane-type pentacyclic triterpenoid with the molecular formula C₃₀H₄₈O₄ [1,2]. It is primarily derived from *Lagerstroemia speciosa* (Banaba), although it has also been isolated from other plants, including Japanese loquat and cranberry-related species [2,3]. Banaba has long been used in folk medicine, particularly in Southeast Asia, for the treatment of diabetes and related metabolic disorders, and corosolic acid has become one of the principal marker compounds used to standardize Banaba-derived products [2,3].

The growing popularity of corosolic acid as a health supplement is largely based on its reported metabolic effects. Experimental and clinical studies have suggested that corosolic acid may lower blood glucose through multiple mechanisms, including enhanced cellular glucose uptake, improved insulin sensitivity, inhibition of α -glucosidase-mediated carbohydrate digestion, and suppression of hepatic gluconeogenesis [1-3]. In addition, corosolic acid has been reported to exhibit anti-obesity, antihyperlipidemic, antioxidant, and anti-inflammatory effects, further supporting its commercialization as a “natural” supplement for glycemic control and weight management [1-3].

Despite these proposed benefits, the clinical safety profile of corosolic acid remains insufficiently defined. Available human studies have generally been small and short-term and were not designed to detect uncommon but serious adverse events [1,3]. Nutraceutical products are also regulated less rigorously than

prescription drugs, raising concerns about inconsistent product quality, variable active ingredient content, inaccurate labeling, and impurities or contaminants [1]. These limitations are particularly relevant in patients with diabetes, polypharmacy, acute intercurrent illness, or reduced renal reserve.

Here, we report a case of severe acute kidney injury (AKI) temporally associated with ingestion of a corosolic acid-containing supplement in a patient with type 2 diabetes mellitus. Clinical evidence linking corosolic acid to renal and metabolic toxicity remains limited, and only a few reports have raised this concern [3,4]. To assess biologic plausibility, we also performed exploratory *in vitro* experiments using HK-2 human proximal tubular epithelial cells to determine whether corosolic acid can induce tubular cytotoxicity and oxidative stress.

3. Case Presentation

A 66-year-old man presented to the emergency department with persistent nausea, vomiting, poor oral intake, and watery diarrhea. He had a history of type 2 diabetes mellitus, hypertension, and remote pulmonary tuberculosis. His regular medications included teneligliptin, pioglitazone, glimepiride/metformin, amlodipine/valsartan, rosuvastatin/ezetimibe, and dapagliflozin.

He reported that after consuming holiday food and alcohol 1 week before presentation, he developed nausea and vomiting the following day and was barely able to eat thereafter. Three days before presentation, he also developed watery diarrhea. At a local clinic immediately before transfer to our hospital, laboratory testing showed severe azotemia, with a blood urea nitrogen (BUN) level of 82 mg/dL, a serum creatinine (Cr) level of 13.2 mg/dL, and an estimated glomerular filtration rate (eGFR) of 4 mL/min/1.73 m².

On admission, his blood pressure was 192/82 mmHg with a pulse rate of 89 beats/min. He had no generalized edema and denied abdominal pain or fever. Initial laboratory tests showed BUN/Cr of 101/14.6 mg/dL, sodium 123 mEq/L, potassium 5.5 mEq/L, calcium 8.3 mg/dL, phosphorus 11.2 mg/dL, uric acid 13.4 mg/dL, venous pH 7.294, bicarbonate 16.4 mmol/L, anion gap 22.5 mmol/L, and lactate 5.4 mmol/L. Serum osmolality was 295 mOsm/kg. Urinalysis showed a specific gravity of 1.009, pH 5.5, protein 2+, positive for glucose, negative for ketones, numerous red blood cells, and 0–1 white blood cells per high-power field. Additional laboratory findings included an erythrocyte sedimentation rate of 70 mm/h, a C-reactive protein level of 0.75 mg/dL, an HbA1c level of 9.2%, and a serum ketone body level of 1.0 mmol/L. Abdominal computed tomography showed no significant renal abnormality or hydronephrosis, although mild pancolitis was noted. Kidney ultrasonography demonstrated normal-sized kidneys (right, 11.2 cm; left, 12.1 cm) with preserved echogenicity and increased resistive indices, supporting AKI rather than chronic structural kidney disease. His renal function had been normal 5 months earlier, with a BUN level of 16 mg/dL, a serum creatinine level of 0.97 mg/dL, and an eGFR of 78 mL/min/1.73 m².

A detailed medication review revealed that he had started taking a health supplement, Nifgen Spike, 15 days before presentation for glycemic control and had continued taking it until the morning of admission. The supplement was discontinued after presentation to our hospital. The active ingredient of this supplement was identified as corosolic acid.

On admission, he was oliguric, with a urine output of less than 400 mL/day. Because of severe AKI with metabolic acidosis and oliguria, hemodialysis was initiated on hospital day 0 and performed on hospital days 0, 1, 2, and 4 (four sessions in total). After the third session (day 2), urine output increased to 700 mL/day, and by hospital day 4 it exceeded 1,000 mL/day. After the fourth session, laboratory values improved to BUN/Cr 53.9/7.04 mg/dL, sodium/potassium 128/4.0 mEq/L, phosphorus 5.3 mg/dL, uric acid 4.4 mg/dL, and lactate 1.3 mmol/L, and hemodialysis was discontinued. After 2 weeks of hospitalization, BUN/Cr had improved to 33.5/1.53 mg/dL, with an eGFR of 45.8 mL/min/1.73 m², and urine output exceeded 2,000 mL/day. He was discharged on hospital day 16. At the first outpatient follow-up visit, 25 days after admission, BUN/Cr was 15.9/1.2 mg/dL and eGFR was 60.6 mL/min/1.73 m².

Given the abrupt decline from previously normal renal function, the severe gastrointestinal fluid loss, the concomitant use of medications that may increase susceptibility to kidney injury, and the temporal relationship with recent exposure to a corosolic acid-containing supplement, the episode was considered severe AKI of multifactorial origin, with hemodynamic factors likely playing a role. The cell-based experiments described below were performed to assess whether corosolic acid can exert toxicity on proximal tubular epithelial cells in the absence of hemodynamic stress. The overall clinical course is summarized in Figure 1.

4. Materials and Methods

4.1. In Vitro Experimental Design

HK-2 cells were exposed to increasing concentrations of corosolic acid. Cell viability was assessed after 24 and 48 hours across concentrations ranging from 0 to 16 μ M. Based on the viability profile, mechanistic experiments were performed using 0, 4, and 8 μ M corosolic acid. Real-time polymerase chain reaction was performed at 12, 24, and 48 hours to evaluate mRNA expression of lipocalin 2 (LCN2), NADPH oxidase 4 (NOX4), interleukin-1 beta (IL1B), high-mobility group box 1 (HMGB1), catalase, superoxide dismutase 2 (SOD2), heme oxygenase 1 (HMOX1), glutathione peroxidase 4 (GPX4), BCL2-associated X protein (BAX), and BCL2. Western blotting was performed at 24 and 48 hours for GPX4, catalase, NOX4, SOD2, BAX, BCL2, and HMGB1. Statistical comparisons were performed using two-way analysis of variance followed by Tukey's multiple-comparison testing. Primer sequences used for RT-qPCR are provided in Supplementary Table S1.

Figure 1: Clinical course of severe acute kidney injury after exposure to a corosolic acid-containing supplement.

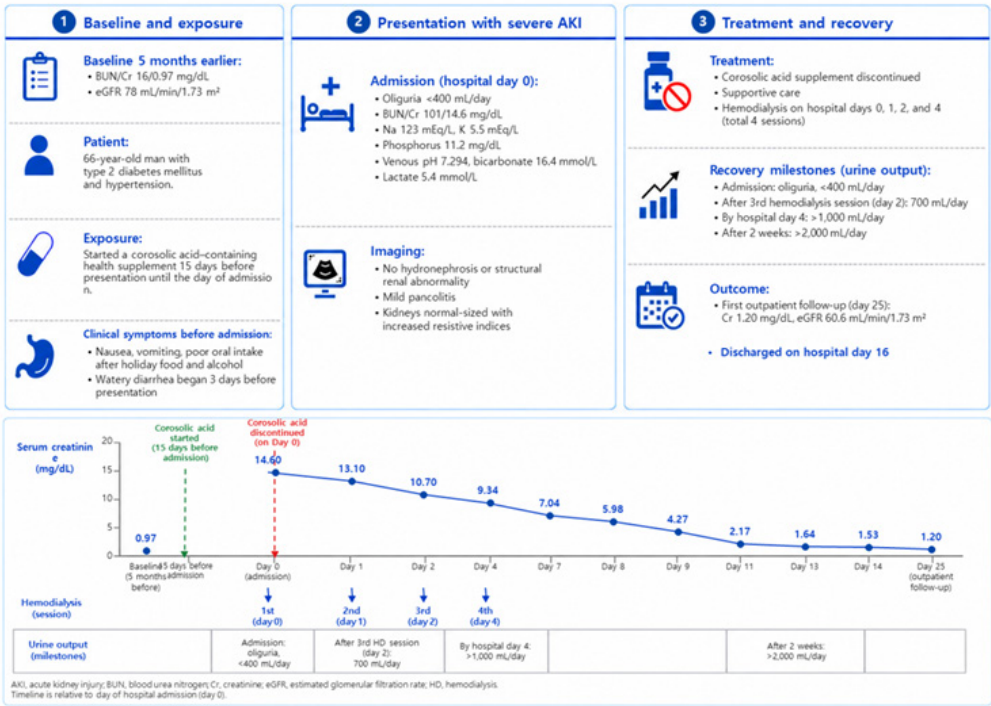


Figure 1: Clinical course of severe acute kidney injury after exposure to a corosolic acid-containing supplement. The supplement was started 15 days before admission, continued until the morning of admission, and discontinued after presentation to the hospital on hospital day 0. Severe AKI with oliguria, hyperkalemia, and metabolic acidosis required four hemodialysis sessions on hospital days 0, 1, 2, and 4, followed by progressive recovery of urine output and renal function. The patient was discharged on hospital day 16, and serum creatinine was 1.20 mg/dL at the first outpatient follow-up on day 25. AKI, acute kidney injury; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; HD, hemodialysis.

Supplementary Table S1: Sequences of real-time RT-PCR primers used in this study.

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
Human NGAL	TGGGCTCCCTGAAAACC	TGTGCACTCAGCCGTCGATA
Human NOX4	AAGCCAGTCACCATCATTTTCG	CTTTGACCATTTCGGATTTC
Human IL-1β	TGAAGCTGATGGCCCTAAACA	GTAGTGGTGGTTCGGAGATTTCG
Human HMGB1	TGAAACCCCGCCTCTAAAA	CCGGGTTCACGCCATTC
Human Catalase	CCAAATACTCCAAGGCAAAGGT	AACCCGATTCTCCAGCAACA
Human SOD2	GCTTGCAAAAAGTAAACCACGAT	CCAGGCTTGATGCACATCTTAG
Human HMOX1	AGGGAAGCCCCACTCAAC	ACTGTCGCCACCAGAAAGCT
Human GPX4	CCGATACGCTGAGTGTGGTTT	GTTACTCCCTGGCTCCTGCTT
Human Bax	GGGGACGAACTGGACAGTAA	CAGTTGAAGTTGCCGTCAGA
Human Bcl-2	ATGTGTGTGGAGAGCGTCAA	ACAGTTCCACAAAGGCATCC
Human GAPDH	TTCACCACCATGGAGAAGGCT	TGGTTCACACCCATGACGAAC

GAPDH was used as the endogenous reference control.

5. Results

5.1. Cell Viability and Tubular Injury Response

Corosolic acid produced a concentration-dependent cytotoxic effect in HK-2 cells. Cell viability remained largely preserved at 2–6 μM, whereas exposure to 8 μM significantly reduced viability at both 24 and 48 hours ($P < 0.001$ versus the respective vehicle control). A steep decline in viability was observed at concentrations of 10 μM or higher, indicating a threshold-like increase in cytotoxicity between 8 and 10 μM. These findings demonstrate that corosolic acid can directly impair the survival of proximal tubular epithelial cells in the absence of systemic hemodynamic or metabolic confounders.

LCN2 mRNA, which encodes neutrophil gelatinase-associated lipocalin (NGAL), was markedly increased by corosolic acid, with a concentration- and time-dependent increase at 4 and 8 μM. NGAL is a well-established marker of tubular stress and injury, this response suggests that the observed reduction in cell viability reflected cellular injury rather than a nonspecific alteration in metabolic activity.

5.2. Oxidative-Stress and Cell-Death Signaling

Corosolic acid induced an oxidative-stress response. NOX4 mRNA increased prominently at 8 μM, particularly at 24 hours, and NOX4 protein was increased at 8 μM at both 24 and 48

hours. HMOX1 and SOD2 mRNA were also upregulated, whereas catalase mRNA decreased. Western blotting showed increased SOD2 and reduced catalase protein, consistent with an imbalance between reactive oxygen species (ROS) generation and antioxidant detoxification. HMGB1 mRNA expression increased with corosolic acid exposure, although intracellular HMGB1 protein levels did not increase consistently.

GPX4 showed a distinct pattern. GPX4 mRNA expression decreased at 8 μ M after 24 hours but rebounded at 48 hours,

whereas GPX4 protein levels decreased at both 4 and 8 μ M, with the greatest reduction at 8 μ M after 48 hours. This discordance between mRNA and protein suggests that transcriptional compensation may be insufficient to preserve GPX4 protein abundance during sustained exposure. In contrast, the BAX/BCL2 ratio did not increase and was lower at 8 μ M. Taken together, the injury was characterized by oxidative stress and loss of GPX4 protein rather than by a BAX/BCL2-mediated apoptotic shift. The principal *in vitro* findings are summarized in Figures 2-4.

Figure 2. Cytotoxic effects of corosolic acid on HK-2 cells

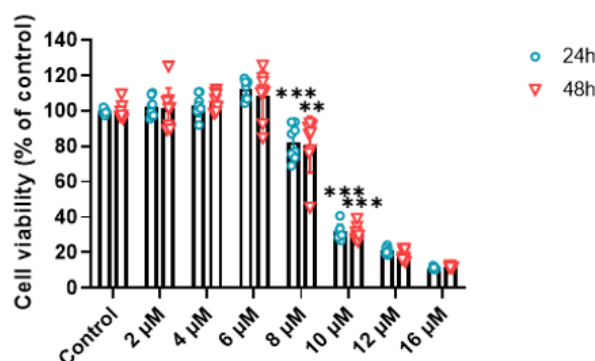


Figure 2: HK-2 cells were exposed to increasing concentrations of corosolic acid (0–16 μ M) for 24 or 48 hours. Cell viability is expressed as a percentage of the respective vehicle control. Viability was largely preserved at 2–6 μ M, decreased significantly at 8 μ M, and declined markedly at concentrations of 10 μ M or higher. Statistical significance was analyzed by two-way ANOVA followed by Tukey's multiple-comparisons test (***p* < 0.001 vs. the respective control).

Figure 3. Real-time RT-qPCR analysis of corosolic acid-induced tubular stress and oxidative-response signaling in HK-2 cells

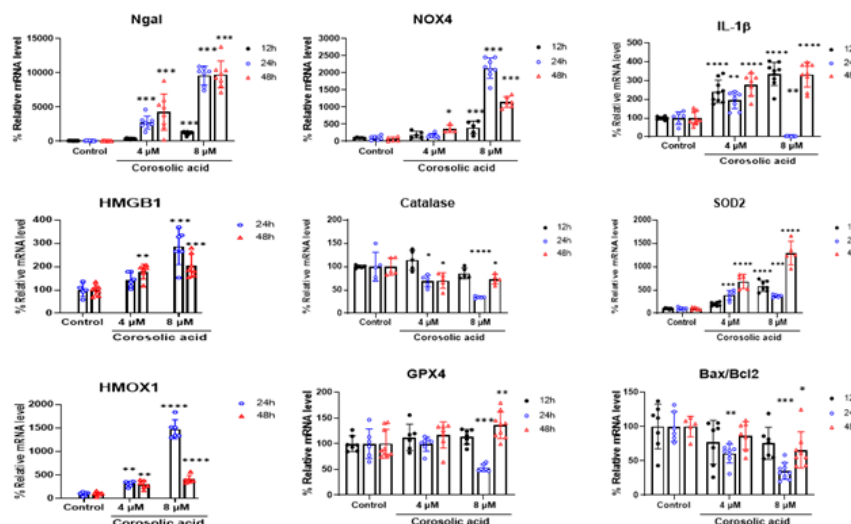


Figure 3: Relative mRNA expression of LCN2 (NGAL), NOX4, IL1 β , HMGB1, catalase, SOD2, HMOX1, GPX4, and BAX/BCL2 was assessed after exposure to corosolic acid (0, 4, or 8 μ M) for 12, 24, and 48 hours. Corosolic acid induced marked tubular injury and oxidative-stress responses, including increased LCN2, NOX4, HMOX1, SOD2, and HMGB1 expression and reduced catalase expression. GPX4 mRNA showed a transient decrease at 8 μ M after 24 hours with recovery at 48 hours, whereas the BAX/BCL2 ratio showed no consistent pro-apoptotic increase. Statistical comparisons were performed using two-way ANOVA followed by Tukey's post hoc test for simple effects within each time point (***P* < 0.001 versus the respective vehicle control group at each time point).

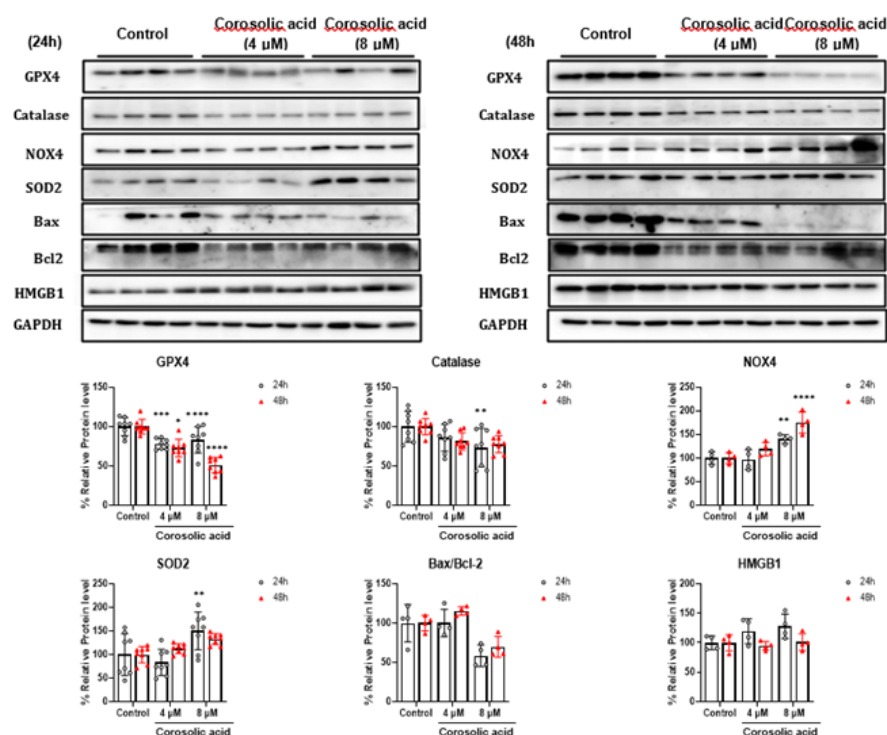
Figure 4. Western blot analysis of oxidative-stress and cell-death-related proteins in HK-2 cells

Figure 4: Representative immunoblots and densitometric quantification of GPX4, catalase, NOX4, SOD2, BAX/BCL2, and HMGB1 are shown after 24 and 48 hours of exposure to corosolic acid (4 or 8 μM), with GAPDH used as the loading control. Corosolic acid was associated with reduced GPX4 and catalase expression and increased NOX4 and SOD2 expression, particularly at 8 μM. The BAX/BCL2 ratio did not demonstrate a pro-apoptotic increase. Statistical comparisons were performed using two-way ANOVA followed by Tukey's post hoc test for simple effects within columns (*P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001 versus the respective vehicle control group within each time point).

6. Discussion

This case highlights a potential safety issue related to corosolic acid-containing supplements. Corosolic acid is widely marketed as a nutraceutical for glycemic control, but its clinical safety profile remains insufficiently defined and previous clinical reports have not established it as nephrotoxin. The present report adds a new layer of evidence: in addition to the temporal association between supplement exposure and severe AKI, corosolic acid reduced viability and induced a tubular injury response in HK-2 cells. These in vitro findings do not establish that the patient's renal tissue was exposed to comparable concentrations; they indicate only that corosolic acid can be cytotoxic to tubular cells independent of dehydration or concomitant medications.

The molecular pattern observed in HK-2 cells provides a biologically plausible mechanism for tubular injury. Increased NOX4 together with induction of HMOX1 and SOD2 is consistent with an oxidative-stress response, while the reduction in catalase suggests impaired peroxide detoxification. Most importantly, GPX4 protein progressively decreased despite partial recovery of GPX4 mRNA at 48 hours, indicating loss of a key lipid-peroxide defense mechanism and the concurrent induction of LCN2 is consistent with a tubular stress phenotype. Taken together, these findings suggest that corosolic acid can shift proximal tubular cells toward an oxidant-dominant state and impair antioxidant defenses, thereby lowering the threshold for cell injury and death.

Because GPX4 is a central suppressor of ferroptosis, an iron-dependent form of regulated cell death driven by excessive membrane lipid peroxidation [5], the reduction in GPX4 protein raises the possibility that ferroptosis-related pathways contribute to corosolic acid-induced tubular injury. Nevertheless, the evidence should not be overinterpreted. GPX4 reduction and oxidative stress are not sufficient to establish ferroptosis, and apoptosis, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, necrosis or mixed regulated cell-death pathways remain possible. Functional studies are warranted, including direct measurement of lipid peroxidation and the use of pathway-specific inhibitors such as ferrostatin-1. Ferroptosis therefore remains a mechanistically plausible hypothesis generated by the current data rather than a proven explanation.

The clinical episode had major hemodynamic contributors. Persistent nausea and vomiting, watery diarrhea, markedly decreased oral intake, and recent alcohol consumption could each have caused intravascular volume depletion and renal hypoperfusion, and these factors alone may account for a substantial part of the renal injury. However, the severity of the injury, which required four sessions of hemodialysis, and the temporal relationship with supplement use raise the question of an additional insult. The tubular toxicity observed in vitro offers a biologically plausible mechanism by which corosolic acid could have acted as a second hit in an already hypoperfused kidney, although its actual contribution cannot be quantified in a single case. The

patient's chronic medications may also have increased susceptibility to hemodynamic kidney injury. SGLT2 inhibitors exert an osmotic diuretic effect through glycosuria and natriuresis, and temporary discontinuation is recommended during acute illness or conditions associated with fluid loss, including diarrheal illness [6,7].

Renin-angiotensin system blockers are not intrinsically nephrotoxic; however, during dehydration or volume depletion, they may contribute to a further decline in glomerular filtration by reducing angiotensin II-mediated efferent arteriolar constriction [8].

A 2010 report described a patient with diabetes and impaired kidney function who developed AKI after taking corosolic acid [4]. Although that report raised concern that corosolic acid may have contributed to AKI, the evidence was based primarily on the clinical presentation and temporal association, and no direct experimental evidence of corosolic acid-induced renal toxicity was provided. The patient also had chronic kidney disease and had taken diclofenac for 1 week, making concomitant NSAID-associated renal hypoperfusion an important alternative contributor [4]. Thus, although the previous report suggested a possible nephrotoxic role of corosolic acid, the underlying renal mechanism remained uncertain. This case differs in that baseline renal function had been normal 5 months earlier, but it similarly involved major prerenal stressors, an abrupt severe decline in kidney function, and recent corosolic acid exposure. The accompanying *in vitro* findings extend the earlier clinical observation by showing that corosolic acid can injure human proximal tubular epithelial cells under experimental conditions.

Another important issue is the unpredictability of systemic exposure during real-world supplement use. Corosolic acid has low water solubility and low oral bioavailability and undergoes hepatic metabolism involving CYP1A2, CYP3A4, glucuronidation, and acetylation pathways [1,2]. In commercial products, the delivered dose may vary depending on extraction methods, formulation, and manufacturing quality. In this case, neither the actual corosolic acid content of the consumed product nor the patient's circulating corosolic acid concentration was measured. Therefore, the concentration used *in vitro* cannot be translated to tubular exposure in the patient.

The available efficacy literature does not resolve these safety concerns. Banaba and corosolic acid have long been used in folk medicine for diabetes, and small human studies have reported reductions in fasting or postprandial glucose after administration of Banaba extract or corosolic acid-containing preparations [1,3]. However, those studies were generally small, short-term, and not designed to assess renal outcomes or detect uncommon but serious adverse events. Notably, a prior report published in 2010 raised concern for corosolic acid-associated nephrotoxicity [4], although a subsequent review concluded that the causal role of corosolic acid remained unclear [3]. The present case and supporting cell data do not establish population-level risk,

but they provide a stronger rationale for systematic renal safety evaluation.

Preclinical studies have also suggested potentially renoprotective effects of corosolic acid in experimental diabetic nephropathy models, including inhibition of glomerular mesangial cell proliferation and attenuation of albuminuria, mesangial expansion, and renal fibrosis [9, 10]. However, these studies were conducted primarily in chronic diabetic and glomerular injury models and did not evaluate acute toxicity in tubular epithelial cells. In contrast, in this HK-2 model, increasing corosolic acid concentrations produced concentration-dependent loss of cell viability accompanied by evidence of oxidative tubular injury under the experimental conditions. Thus, the previously reported renoprotective effects in diabetic models do not preclude direct tubular toxicity of corosolic acid.

A notable strength of our study is the integration of *in vitro* mechanistic experiments with the observed clinical course; nonetheless, several limitations should be noted. First, the actual corosolic acid content of the supplement and circulating drug concentration were unavailable, and no rechallenge was attempted. Second, the HK-2 experiments showed direct cellular toxicity only under the tested *in vitro* conditions; they do not establish that comparable renal concentrations were achieved in this patient. Third, kidney biopsy was not performed, precluding direct assessment of renal histopathology and tissue expression of relevant markers, including GPX4. Fourth, although GPX4 depletion and oxidative-stress signaling suggest possible ferroptotic involvement, ferroptosis was not directly demonstrated.

Despite these limitations, the convergence of clinical dechallenge and experimentally demonstrated tubular injury provides biological plausibility for a nephrotoxic contribution of corosolic acid. Clinicians should therefore consider non-prescription supplements when evaluating otherwise unexplained or disproportionately severe AKI, particularly during acute illness or volume depletion.

7. Conclusion

We report severe, dialysis-requiring AKI temporally associated with a corosolic acid-containing supplement. Although volume depletion and hemodynamic factors likely contributed, corosolic acid induced direct, concentration-dependent proximal tubular cytotoxicity, oxidative stress, and loss of GPX4-dependent antioxidant defense in HK-2 cells. These findings support a potential nephrotoxic contribution of corosolic acid. Clinicians should consider supplement exposure in otherwise unexplained severe AKI, particularly during acute illness or volume depletion. Further studies are needed to clarify the renal safety of corosolic acid-containing products.

8. Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and accompanying clinical information.

9. Acknowledgments

The authors gratefully acknowledge the patient for granting permission to publish this case report.

10. Conflict of Interest

The authors declare no conflicts of interest.

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