
# Glucosamine/cranberry /Ginseng


- By Dr.maryam Mohammadi assistant professor of Zahedan Univercity

## Glucosamine is a commonly used alternative therapy in OA

- ✓ Glucosamine is an aminosaccharide derived from chitin that takes part in the synthesis of glycosaminoglycans and proteoglycans by chondrocytes/ substrate for the biosynthesis of chondroitin sulfate, hyaluronic acid and other macromolecules located in the cartilage matrix.


Glucosamine sulfate (GS) actions:

- ✓ Inhibits the degradation of proteoglycans (the ground substance of articular cartilage)
- ✓ Rebuilds experimentally induced cartilaginous damage
- ✓ Chondroprotective and antiarthritic effects
- ✓ stimulation of proteoglycan synthesis / dose dependent

Glucosamine sulfate has very mild anti-inflammatory and anti-reactive effects on edema-provoking agents including carrageenan, dextran, acetic acid, and formalin.

✓Glucosamine sulfate has been shown the blood-synovial barrier.

lower serum concentrations than with parenteral use/ orally administered glucosamine sulfate has near-identical pharmacokinetics after the first-pass effect of the liver:


✓ Clearance primarily via the lungs (~50%) as carbon dioxide

kidney (~35%)

feces (~2%)

✓ side effects of glucosamine: worsening insulin resistance in diabetics

✓There is no available literature reporting a direct link between glucosamine and nephrotoxicity**???**

✓ There have been reports stating that additives like aristolochic acid, used in the preparation of glucosamine, can be nephrotoxic.

- ✓ Drug-induced acute TIN is an inflammatory process involving the tubules and the space between the tubules and the glomeruli.


- ✓ It is mediated by T cell hypersensitivity reaction and cytotoxic T cell injury.
- ✓ Renal biopsy is the gold standard for diagnosis.
- ✓ Stopping the suspected medication forms the main component of treatment, with most patients recovering rapidly on withdrawal of the offending drug.
- ✓ Corticosteroid and immunosuppressants, in cases where there is no significant improvement in the renal function, may be of value.
- ✓ Recovery is more rapid in those individuals who have been exposed to the drug for less than 2 weeks, in comparison with those who have taken the suspected medication for more than 3 weeks.

✓Some experimental animal studies have shown glucosamine can cause apoptosis in kidney tubular and mesangial cells as well as overexpression :

transforming growth factor β1 (TGF-β1)

connective-tissue growth factor (CTGF)

✓ potent inducers of mesangial and interstitial tubulointerstitial fibrosis.

# Chronic tubulointerstitial nephropathy induced by glucosamine: a case report and literature review

Serigne Gueye [1], Morgane Saint-Cricq, Moussa Coulibaly, Nabila Goumri, Céline Guilbeau-Frugier, Hurlot Quentin, Etienne Ged, Abdellatif Sidi Aly, Lionel Rostaing

- ✓ case report: 67-year-old patient who presented with non-proteinuric renal insufficiency and a reduction of the glomerularfiltration rate (GFR) from 86 to 46 mL/min within 3 months.
- ✓ A kidney biopsy showed noninflammatory 40 - 50% fibrosis of the renal cortex associated with acute tubular necrosis.
- ✓ The etiological investigation was negative apart from taking 1,200 mg of glucosamine daily for 3 years to treat osteoarthritic knee pain.
- ✓ Three weeks after stopping glucosamine, GFR increased from 47.5 to 60 mL/min.
- ✓ Reintroduction of glucosamine resulted in loss of kidney function after 3 weeks, with GFR reduced from 60 to 53 mL/ min.
- ✓ glucosamine was shown to cause renal toxicity.

# Acute interstitial nephritis induced by glucosamine

FREE

Vinod Kumar Audimoolam ✉, Sunil Bhandari

*Nephrology Dialysis Transplantation*, Volume 21, Issue 7, July 2006, Page 2031,

✓ Case report:75-year-old man history of difficulty in passing urine, urgency, nocturia and hesitancy. history of fever, rash or arthralgia negative. Past history was uneventful; he denied known drug allergy and the only medication he had been exposed to had been glucosamine (2–3 months) used for treatment of his osteoarthritis.

General and systemic examination was unremarkable except for dehydration ✓

Hb=10.3mg/dL ✓

WBC=15100 ✓

Na=140mmol/l ✓

K=4.3mmol/l ✓

Urea=45.8mmol/l ✓

LFT=normal ✓

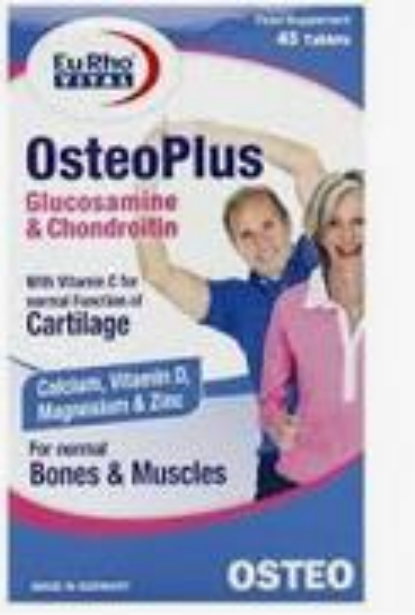
CRP=221mg/l ✓

- ✓ He was initially fluid-resuscitated aggressively and catheterized, draining approximately 2000 ml of urine.
- ✓ Despite the above, his renal functions deteriorated.
- ✓ During the same period, he also had a series of blood tests which included normal complement and negative serum electrophoresis, auto-immune screen, ANCA and anti-GBMDuring the same period, he also had a series of blood tests which included normal complement and negative serum electrophoresis, auto-immune screen, ANCA and anti-GBM.
- ✓ Ultrasound demonstrated normal sized kidneys with good cortical thickness and a simple cyst in the left kidney.
- ✓ Prostatic volume was mildly increased at 48 $cm^3$ and prostatic specific antigen was within normal limits.
- ✓ Renal biopsy demonstrated a heavy mixed inflammatory cell infiltrate within the interstitium, suggestive of **acute TIN**.
- ✓ A minor degree of age-related atherosclerosis, involving the small and slightly larger blood vessels, was also noted.
- ✓ Glucosamine was discontinued and the patient received haemodialysis along with a short course of steroids.
- ✓ His symptoms improved significantly and he was dialysis-independent on discharge

# The chronic effects of glucosamine sulfate (GS) on kidney in Albino Mice

January 2017

Project: The chronic effects of glucosamine sulfate (GS) on kidney in Albino Mice




- ✓ Experimental animals study:
- ✓ 30 Swiss male mice Mus musculus were involved in this study with one month age, they were divided into 3 subgroups (10 animals each).
- ✓ Each group was placed into a clean cage and provided with food and water
- ✓ Animals weight was measured before experiments, treatment was as the following:
  G1: Control group: treated with oral administration of normal saline (0.1) ml for (6, 12)weeks.
  G2: treated with oral glucosamine sulfate with (2500) mg/ kg for (6, 12) week.
  G3: treated with oral glucosamine sulfate(3500) mg/kg with concentration ml for (6, 12) weeks.
- ✓

## ✓ RESULTS AND DISCUSSION

- ✓ Weight changes : there was a difference in the mean weight of the kidneys of the groups treated with glucosamine sulfate compared to the control group.

- ✓ After 6 weeks of the dosage, the statistical results showed a significant decrease in the mean weight of all concentrations (2500, 3500 mg/kg) the decrease value for kidney weight (0.224±0.007) mg/kg at concentration (3500) mg / kg compared to the control group .

- ✓ The results showed that after a period of 12 weeks of the dosage, there was an insignificant increase in the kidney weight of the treated groups.

**Table 1:** Effect of glucosamine sulfate in the mean weight of kidney after (6, 12)weeks.

| Type / Concentration | Kidney weight after (6) weeks | Kidney weight after (12) weeks | P-Value |
|---|---|---|---|
| Control | 0.272 Aa ± 0.004 | 0.189 Bb ± 0.004 | 0.000 |
| 2500 (mg/kg) | 0.225 Ab ± 0.018 | 0.251 Aa ± 0.005 | 0.234 |
| 3500 (mg/kg) | 0.224 Ab ± 0.007 | 0.197 Ab ± 0.009 | 0.078 |
| LSD P ≤ 0.05 | 0.040 | 0.022 | |

Capital and small letter s indicate to comparison in row and column respectively, similar letters are non-significantly differences between means at ($p \leq 0.05$), using LSD test.

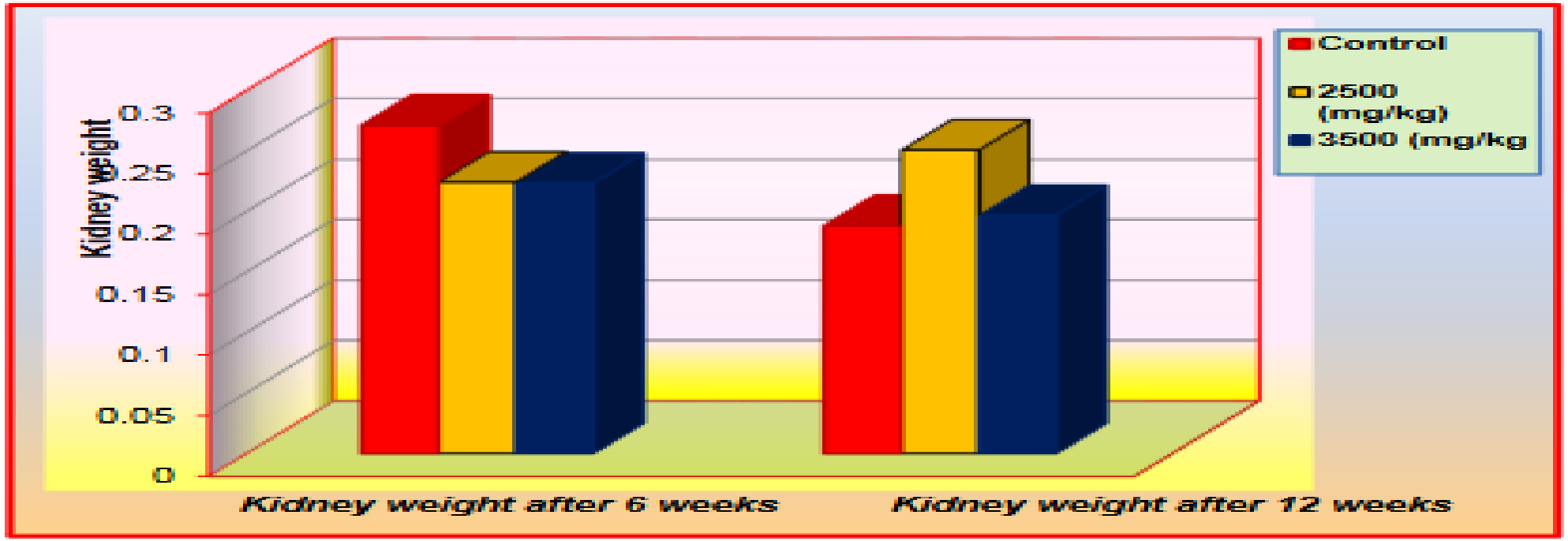



**Figure 1:** Histogram showing effect of treatment with glucosamine sulfate (2500, 3500) mg/kg For (6, 12) weeks with control groups

glucose/ insulin resistance and hyperglycaemia through the effect on the secretion of insulin

↓

decrease in insulin leads to changes in metabolism Fats, carbohydrates and protein

↓

decrease in the entry of glucose to the cells then increase the level of sugar in the serum

↓

activation of the calcification of the liver and muscle and then loss of total body weight or

↓

decrease in weight due to changes in tissue Such as necrosis, atrophy and Shrinkage of glomerular which lead to reduction in the average of weights for the groups treated with GS.

**Histological changes:**

treated groups (2500, 3500) mg/kg of orally glucosamine sulfate(GS) during (6 weeks):

- ✓ inflammatory cell infiltration
- ✓ congestion in veins
- ✓ hydropic degeneration in renal tubules .

- ✓ silver : thickening in most basal membranes of the renal tubules.

## histological changes :

treated groups (2500, 3500) mg/kg of glucosamine sulfate during (12 weeks)

- ✓infiltration & congestion
- ✓ amyloid & shrinkage of glomerular
- ✓pyknotic nuclei of renal tubules cells
- ✓Atrophy in Collecting tubules of kidney
- ✓ necrosis in glomerular of kidney

✓ statistical analysis results after the passage of (12) weeks of the dosage/significant increase in kidney weight of the groups treated with the drug

✓ this increase may occur due to tissue damage caused by the drug such as amyloid increase deposition the protein breakdown as well as amino acids degeneration

taken chronically  GS on the kidney tissue of thereated animal groups:

congestion in the blood vessels supplying the kidneys

↓

infiltration of the inflammation cells

↓

acute inflammation  changes in the flow of blood in the vessels

↓

relaxes and expands in those vessels

↓

accumulation of inside blood

infiltration: increased vascular permeability


shrinkage of glomerulus

leads to reduced blood flow to the glomerulus

reduce the proportion of the drug because it is removed by the Bowman and renal tubules.

- ✓ Another important tissue change : amyloid chang in glomerulus.

- ✓ Damage of cells/synthesis of abnormal proteins resulting from the decomposition of amino acids, especially the immune globules and carbohydrates .

- ✓ drug : sulfur compounds (So4) / rise in blood plasma occurs an increase in the breakdown of proteins as well as sulfuric acid .

## Hydropic degeneration

due to toxins that inhibits the process of glycolysis

↓

decreases in certain substances/ inhibits oxidative phosphorylation

↓

decrease in ATP production/ failure of sodium and potassium pumps

↓

flow of sodium and water into the cells and the

↓

release of potassium from them lead to mitochondria and the internal plasma network that follows the

↓

separation of ribosomes

↓

cytoplasm is filled with irregular large vacuoles

- ✓ Adaptation renal tubules of the kidneys through the atrophy of these cells / defense against the toxicity of the drug and the expansion of cavities / Since cell atrophy is a way for the cell to stay alive as much as possible.

- ✓ The life-chemical mechanism of this condition: process of synthesis and non-synthesis of proteins as there is a balance of protein synthesis and analysis within the cell.

- ✓ Increase in the process of protein degradation leads destruction Catabolism and occurrence of atrophy/ release of these enzymes, the situation inside the cells is not easy, but increases in cases of disorder that occurs inside the cells.

- ✓ The first phase of necrosis :pyknosis phase in the nucleus of the renal tubules cells, which may be due to the damage caused by the drug .

✓Glycogen accumulation renal tubules and the thickening of most basal membranes of the renal tubules due to the toxic effect of the drug on the renal tubule .

The drug damage to various organs in the body, including liver and kidney failure/ synthesis of the drug glucose sulfate is the sulfate group and rise in blood plasma level leads to a case Kidney failure

## CONCLUSION

- ✓ The present study investigated that the GS affected on the glomerular and renal tubules of kidney, and causes histopathological changes and impaired renal function.

- ✓ Degree of influence depended on the concentration of the toxic dose/ pathogenesis of (TIN).

- ✓ Acute interstitial nephritis is an important cause of acute renal dysfunction causes by drugs.


PURECO
CRANBERRY
CONCENTRATE
Product


Ocean Spray
ORIGINAL
Cranberry

# cranberry

# Safety of Cranberry: Evaluation of Evidence of Kidney Stone Formation and Botanical Drug–Interactions

Emily Madden [1], Caleb McLachlan [2], Hellen Oketch-Rabah [1], Angela I Calderón [2 3]

- ✓ cranberry ( *Vaccinium macrocarpon* Aiton) is a fruit native to North America .
- ✓ cranberries / medicinal properties /bladder and kidneys due to urine acidification.
- ✓ Subsequent research confirmed this phenomenon and attributed it to the benzoic acid found in cranberries.
- ✓ The theory postulated that the benzoic acid was being converted into hippuric acid *in vivo* and thus lowered the pH of urine.
- ✓ Researchers : production of hippuric acid was enough to be considered bacteriostatic .
- ✓ 1959 article published by Bodel et al, showed that cranberries were not a rich enough source of benzoic acid for the resulting hippuric acid to be bacteriostatic.

mechanism: preventing microbial adhesion.

- ✓ PACs/ proanthocyanidin-A found in cranberry: which exhibits potent *in vitro* anti-adhesion bioactivity and is thought to be responsible for interfering with bacterial adhesion to the epithelial cells of the urinary tract

- ✓ This is why cranberry products are largely used today to prevent UTIs although persuasive clinical evidence is still lacking**?**

- ✓ prevention of UTIs to its effects on cardiovascular risk factors, metabolic syndrome, gut microbiota, and cancer prevention .

- ✓ Cranberry and its phytochemicals are suggested to have anticancer properties and protective effects against vascular diseases .

- ✓ Research has a program that conducts research on prevention and management of bacterial diseases, including UTIs, stomach ulcers, and periodontal disease **.**

- ✓ Cranberry is a popular ingredient in dietary supplements in the U.S. and is commonly used for preventing urinary tract infections.

- ✓ U.S. Pharmacopeial Convention concluded that cranberry ingredients are not known to be associated with serious risks to human health when consumed properly in dietary supplements / admitted for standard development.

- ✓ Although published clinical and animal data indicated that cranberry is not associated with serious adverse effects/ interactions with warfarin and kidney stone formation were identified as potential risks.

- ✓ Studies have reported contradictory data regarding the role of cranberry in kidney stone formation, with some reports suggesting cranberry is associated with a reduced risk of kidney stones???

- ✓ Interactions with warfarin were not associated with moderate intakes of cranberry juice (240–480 mL).

- ✓ Some reports suggested that the potential for warfarin interactions requires excessive intakes of cranberry juice (1–2 L/day) or cranberry extracts (3000 mg/day).

- ✓ Cases of warfarin interactions with cranberry have mostly involved patients with serious illnesses and/or individuals taking concomitant medications.

- ✓ U.S. Pharmacopeial Convention concluded that the use of cautionary labeling statements regarding interactions with warfarin or kidney stone formation is not necessary in the development of quality standards for cranberry ingredients

# ✓Kidney Stone Formation and Cranberry

- ✓Human clinical studies have reported contradictory data about cranberry and its role in kidney stone formation .

- ✓Some studies indicated that individuals with a history of developing uric acid or calcium oxalate stones are at risk when consuming cranberry products .

- ✓ In contrast, other studies have reported that consumption of large amounts of cranberry may reduce kidney stone formation or urinary ionized calcium associated with stone formation .

- ✓.

# case report

- ✓ A 47-year-old man/ history of kidney stones presented with right renal colic and hematuria and a creatinine level of 2.1 mg/dL. Abdominal films revealed multiple kidney stones and distal ureteral and mid ureteral stones. The patient had taken cranberry concentrate tablets twice daily for the previous 6 mo and had no kidney stones 1 year before .
- ✓
- ✓ Kidney stones : consist of calcium oxalate. It was not reported if the patient was taking other supplements or medications at the time.

- ✓ The authors did not report the level of cranberry concentrate in the tablets taken by the patient.
- ✓ Several brands of cranberry concentrate tablets are commercially available and the product label for one commercially available 450 mg tablet of cranberry concentrate (equivalent to 2880 mL of cranberry concentrate juice) includes the recommendation to take the tablet twice daily

- ✓ Clinical study reported :significant increase in urinary oxalate levels in healthy participants given cranberry concentrate tablets for 1 wk (n = 5) , prompting caution that individuals with existing nephrolithiasis might be at increased risk of kidney stone formation when consuming large amounts of cranberry .

- ✓ significant increase in urinary calcium, phosphate, and sodium, along with magnesium and potassium, which are both inhibitors of stone formation.

- ✓ authors proposed : oxalate content in cranberry could cause kidney stone formation; however, the authors did not measure oxalate levels in the cranberry tablets.

- ✓ One report that a 30 mL volume of cranberry juice contains approximately 1.89 mg of oxalate/oxalate content in the tablets was not reported/authors estimated that if the oxalate content was proportional to the volume of cranberry juice in the tablets, then the twice-daily dosing with cranberry tablets containing 450 mg of cranberry concentrate would contain approximately 363 mg of oxalate per day .
- ✓
- ✓ clinical study was criticized for not measuring the content of oxalate in the cranberry concentrate tablets and for not assessing dietary intakes of vitamin C or calcium in the participants, both of which can contribute to urinary oxalates.

One clinical study reported that 500 mL of cranberry juice given to healthy men for 2 wk had shown favorable effects on risk factors for stone formation (n = 20),

decrease in oxalate and phosphate excretion

increase in citrate excretion

decrease in relative supersaturation of calcium oxalate

participants given cranberry juice had significantly higher dietary intakes of oxalate and ascorbic acid ($p = 0.0184$ and $< 0.001$, respectively)/ oxalate and ascorbic acid measured in the cranberry juice (86 mg/mL and 300 mg/L, respectively) compared to control participants given water.

The authors : cranberry juice shows antilithogenic properties.

- ✓ A 7-day clinical study evaluated the effects of consuming 1 L of cranberry juice daily in healthy individuals and those with a history of forming calcium oxalate stones (n = 12 per group) .

- ✓ Cranberry juice significantly increased urinary calcium and urinary oxalate levels, thereby increasing urinary saturation of calcium oxalate by **18%** across treatment groups.
- ✓ urinary citrate was unchanged; urinary magnesium increased slightly; and urinary ammonium, titratable acidity, and net acid excretion increased.

- ✓ Urinary and serum uric acid also decreased, which the authors mentioned could offset the propensity of uric acid crystallization associated with a lower urinary pH.

- ✓ The authors concluded that cranberry juice exerts a mixed impact on the crystallization of kidney-stone-forming salts: while crystallization of calcium oxalate was enhanced, brushite and monosodium urate saturation were reduced.

- ✓ Overall, cranberry juice may not substantially affect kidney stone formation

- ✓ study, healthy male participants given 330 mL of cranberry juice daily for 5 days had decreased urinary pH and increased excretion of oxalic acid and relative supersaturation of uric acid (n = 12).

- ✓ Excretions of citric acid, calcium, magnesium, and uric acid were not significantly altered, and the relative supersaturation for struvite and brushite was decreased but did not reach statistical significance.

- ✓ The increased oxalic acid excretion was proposed to be caused by the oxalic acid content in cranberry juice (167 µmol/L oxalic acid).

- ✓ The authors concluded that since cranberry juice lowers the pH of urine, it could be useful for the treatment of apatite, brushite, and struvite stones as well as urinary tract infections; however, more research is needed in patients with a history of kidney stones .

patients with a history of struvite stones who consumed 2 pints of cranberry juice per day for 9 y

- ✓ No recurrence of stones (60% )
- ✓ No increase of stone size (32%)
- ✓No new stones or an increase in stone size (6%)
- ✓ however/ the study did not include a control group.

# Health Canada monographs :

caution statement for the intake of cranberry in individuals with a history of kidney stones:

**“Consult a health care practitioner/health care provider/health care professional/doctor/physician before use if you have a history of kidney stones”**

2011 ANSES(French Agency for food,Environmental and Occupational Health & safety) opinion:

**“…given the data showing increased urinary excretion of calcium oxalate, long-term consumption of cranberry in individuals prone to oxalate kidney stones is not recommended**

# ESCOP monograph :

- ✓ **cranberry recommends that patients with a history of calcium oxalate stone formation should seek medical advice before taking cranberry**

## ✓FDA CAERS/Canada vigilance program:

✓No AERs suggesting kidney stone formation associated with cranberry products were found in searches of publicly available databases including the FDA CAERS and the Canada Vigilance Program database .

# Ginseng

- ✓Ginseng is a slow-growing, perennial plant with fleshy roots, belonging to the genus Panax of the family Araliaceae.

- ✓ Ginseng is one of the most widely prescribed and intensively studied herbal medicines.
- ✓

- ✓Several studies have indicated benefits of ginseng in the treatment of renal damage and hepatotoxicity.

- ✓Acute kidney injury as an adverse effect has not been reported.

**Case report**:A 43-year-old woman who had consumed 3 roots of ginseng with alcohol some days before:general weakness, myalgia, and oligouria/ hypertension medication for 1 year /undergone surgery for early gastric cancer 3 years ago.

- ✓ She was in an oliguric state (150 mL/day)/massive hydration (3 L/day) was administered /did not increase her urine output
- ✓ Blood test

Ast=5241IU/L(37-10) ✓

Alt=721IU/L(37-10) ✓

LDH=1560IU/L(218-472) ✓

BUN=41mg/dl(8-23) ✓

Cr=4.3mg/dl(0.5-1.3) ✓

FENa=6.6% ✓

IGE=921IU/ML ✓

CBC=5500mm3 ✓

Hb=11.3g/dL ✓

U/A رنگ ادرار زرد -تیره PH-5.8 pro=+3 RBC=+2 WBC=+3 ✓

perform haemodialysis and conducted a renal biopsy

In the biopsy, we found interstitial mononuclear cell infiltration and oedema compatible with **acute interstitial nephritis**

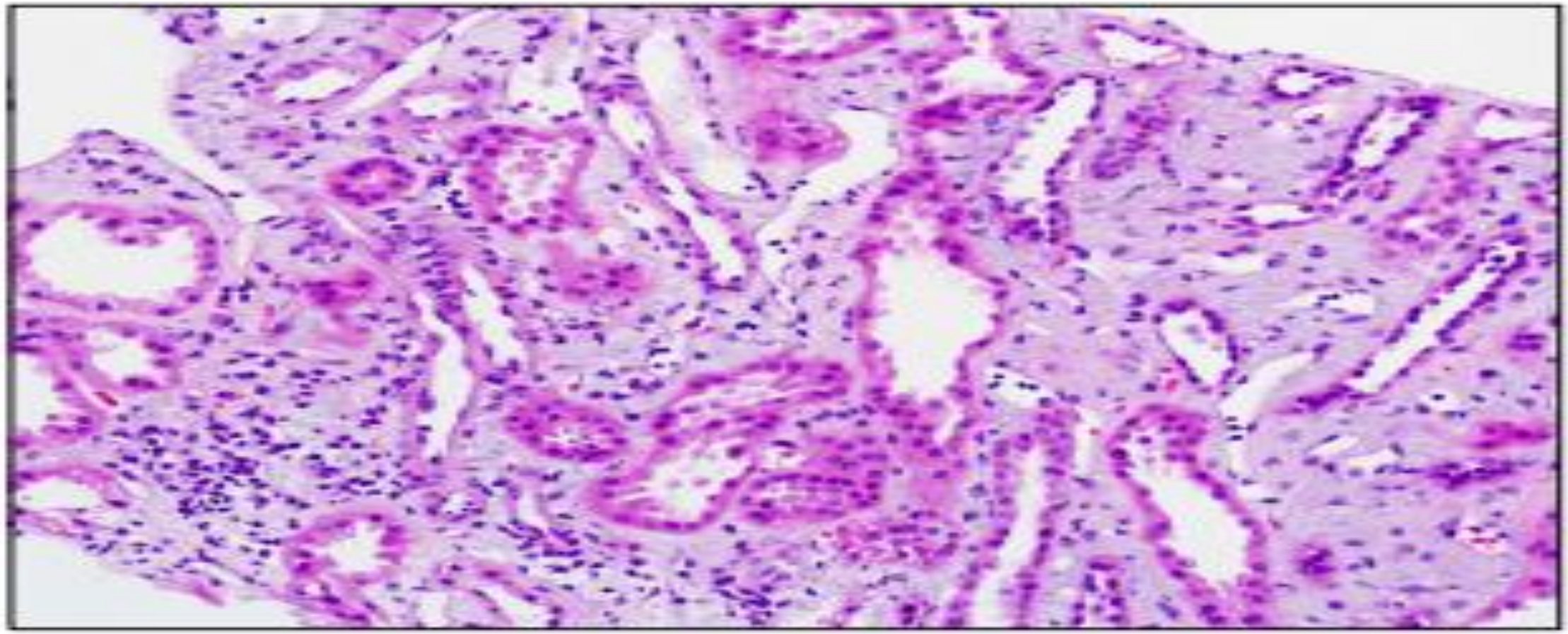


**FIG. 1. Microscopic image shows interstitial mononuclear cell infiltrate with edema (hematoxyline and eosin stain, magnification 200×).**

- ✓ After 5 rounds of haemodialysis, oliguria and oedema also improved.
- ✓ She was discharged from the hospital when she showed normal AST and ALT levels (16 IU/L and 26 IU/L, respectively),
- ✓ improved renal function (BUN: 48.3 mg/dL, Cr: 3.4 mg/dL),
- ✓ and increased urine output (2,930 mL/day).
- ✓ She visited the outpatient clinic after a week.
- ✓ Her renal function test showed completely normal results (BUN: 17.5 mg/dL, Cr: 1.0 mg/dL).

- ✓ The patient ingested ginseng with alcohol and she was dehydrated.
- ✓ It could be hypothesized that dehydration and alcohol consumption resulted in higher susceptibility to kidney and liver damage

- ✓This is the first reported case of acute kidney injury associated with ingestion of ginseng.

- ✓ We emphasize that despite the known benefits of ginseng, it is necessary to ingest it in sufficiently hydrated condition, without concurrent consumption of harmful agents.


# Thank's for your attention