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**Introduction & Objectives:** Epidemiological evidence of over 9,000 people suggests that daily intake of vinegar whose principal bioactive component is acetic acid is associated with a reduced risk of nephrolithiasis. The underlying mechanism, however, remains largely unknown.

**Materials & Methods:** We examined the in vitro and in vivo anti-nephrolithiasis effects of vinegar and acetate. A randomized study was performed to confirm the effects of vinegar in humans.

**Results:** We found individuals with daily consumption of vinegar compared to those without have a higher citrate and a lower calcium excretion in urine, two critical molecules for calcium oxalate (CaOx) kidney stone in humans. We observed that oral administration of vinegar or 5% acetate increased citrate and reduced calcium in urinary excretion, and finally suppressed renal CaOx crystal formation in a rat model. Mechanism dissection suggested that acetate enhanced acetylation of Histone H3 in renal tubular cells and promoted expression of microRNAs-130a-3p, -148b-3p and -374b-5p by increasing H3K9, H3K27 acetylation at their promoter regions. These miRNAs can suppress the expression of Nadc1 and Cldn14, thus enhancing urinary citrate excretion and reducing urinary calcium excretion. Significantly these mechanistic findings were confirmed in human kidney tissues, suggesting similar mechanistic relationships exist in humans. Results from a pilot clinical study indicated that daily intake of vinegar reduced stone recurrence, increased citrate and reduced calcium in urinary excretion in CaOx stone formers without adverse side effects.

**Conclusions:** Vinegar prevents renal CaOx crystal formation through influencing urinary citrate and calcium excretion via epigenetic regulations. Vinegar consumption is a promising strategy to prevent CaOx nephrolithiasis occurrence and recurrence.