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Elucidation of Molecular Mechanism Involved in Nephroprotective Potential of Naringin in Ethylene Glycol-Induced Urolithiasis in Experimental Uninephrectomized Hypertensive Rats

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***SUMMARY*. The objective of present investigation was to evaluate the nephroprotective potential of naringin against ethylene glycol (EG)-induced urolithiasis in experimental uninephrectomized hypertensive rats. EG (0.75% in drinking water) was used to induce urolithiasis in uninephrectomized hypertensive rats. Rats were treated with either naringin (20, 40, and 80 mg/kg, p.o.) for 28 days. Chronic administration of EG resulted in significant alterations ($p < 0.05$) in serum and urinary parameters (urea nitrogen, uric acid, creatinine, sodium, calcium, and LDH) whereas, administration of naringin (40 and 80 mg/kg) significantly attenuated ($p < 0.05$) these alterations. Naringin also significantly attenuated ($p < 0.05$) EG-induced hemodynamic and electrocardiographic abnormalities. Elevated levels of cardiac and renal MDA and nitric oxide and decreased levels of SOD and GSH were significantly restored ($p < 0.05$) by naringin treatment. RT-PCR analysis revealed that naringin significantly inhibited ($p < 0.05$) EG-induced upregulated mRNA expressions of renal KIM-1, NGAL, bikunin, and iNOs as well as down-regulated mRNA expressions of eNOs and OPN. Histological aberrations induced in renal and cardiac tissue after chronic administration of EG was significantly decreased ($p < 0.05$) by naringin. In conclusion, naringin exerts its nephroprotective effect against EG-induced via modulation of elevated oxidative stress and altered renal KIM-1, NGAL, bikunin, iNOs, eNOs, and OPN mRNA expressions.**

RESUMEN. El objetivo de la presente investigación fue evaluar el potencial nefroprotector de la naringina contra la urolitiasis inducida por etilenglicol (EG) en ratas hipertensas no nefrectomizadas experimentales. Se usó EG (0,75% en agua potable) para inducir urolitiasis en ratas hipertensas no nefrectomizadas. Las ratas se trataron con naringina (20, 40 y 80 mg/kg, p.o.) durante 28 días. La administración crónica de EG resultó en alteraciones significativas ($p < 0.05$) en los parámetros séricos y urinarios (nitrógeno ureico, ácido úrico, creatinina, sodio, calcio y LDH) mientras que la administración de naringina (40 y 80 mg/kg) atenuó significativamente ($p < 0.05$) estas alteraciones. La naringina también inhibió significativamente ($p < 0.05$) las alteraciones inducidas por EG en las anomalías hemodinámicas y electrocardiográficas. Los niveles elevados de MDA cardíaca y renal y óxido nítrico y la disminución de los niveles de SOD y GSH se restablecieron significativamente ($p < 0,05$) mediante el tratamiento con naringina. El análisis de RT-PCR reveló que la naringina inhibió significativamente ($p < 0.05$) las expresiones de ARNm reguladas por EG inducidas por KIM-1, NGAL, bikunina e iNOs, así como las expresiones de ARNm reguladas por disminución de eNO y OPN. Las aberraciones histológicas inducidas en el tejido renal y cardíaco después de la administración crónica de EG disminuyeron significativamente ($p < 0.05$) por acción de naringina. En conclusión, naringina ejerce su efecto nefroprotector contra la EG inducida por la modulación del estrés oxidativo elevado y la alteración de la expresión renal de KIM-1, NGAL, bikunina, iNOs, eNOs y ARNm de OPN.

KEY WORDS: bikunin, eNOs, ethylene glycol-induced urolithiasis, iNOs, kidney stone, naringin, osteopontin

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