Journal of Ethnopharmacology 306 (2023) 116157

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Himalayan *Citrus jambhiri* juice reduced renal crystallization in nephrolithiasis by possible inhibition of glycolate oxidase and matrix metalloproteinases

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ARTICLE INFO

Handling Editor: Alexander N. Shikov

Keywords:
Crystallization
Docking
MMP-9
Nephroprotection
Stones

ABSTRACT

Ethnopharmacological relevance: Citrus fruits are a very rich source of electrolytes and citric acid. They have been used traditionally for treating urinary ailments and renal stones. *Citrus jambhiri* is indigenously used as a diuretic.
Aim of the study: Present study aimed at establishing the antiurolithiatic potential of the juice of *Citrus jambhiri* fruits along with the elucidation of the mechanism involved in the urolithiasis disease defying activity.
Methods: The antiurolithiatic activity was established by means of nucleation, growth and aggregation assay in the *in vitro* settings and by means of ethylene glycol mediated calcium oxalate urolithiasis in the male Wistar rats. Docking studies were performed in an attempt to determine the mechanism of the antiurolithiatic action.
Results: Present study revealed the role of *C. jambhiri* fruit juice in reducing nucleation, growth and aggregation of calcium oxalate crystals by possible reduction in the urinary supersaturation relative to calcium oxalate and raising the zeta potential of the calcium oxalate crystals. *C. jambhiri* fruit juice treatment in experimental rats produced significant amelioration of hypercalciuria, hyperoxaluria, hyperphosphaturia, hyperproteinuria, hyperuricosuria, hypocitraturia and hypomagnesiuria and ion activity product of calcium oxalate. It exhibited nephroprotection against calcium oxalate crystals induced renal tubular dilation and renal tissue deterioration. Docking studies further revealed high binding potential of the phytoconstituents of *C. jambhiri* viz. narirutin, neohesperidin, hesperidin, rutin and citric acid with glycolate oxidase and matrix metalloproteinase-9.
Conclusion: C. *jambhiri* fruit juice possesses excellent antiurolithiatic activity. The study reveals antiurolithiatic mechanism that involves restoration of equilibrium between the promoters and inhibitors of stone formation; and inhibition of matrix metalloproteinases and glycolate oxidase.

1. Introduction

Urinary stones or urolithiasis categorically falls under the repertoire of complex diseases (Bawari et al., 2017). Its complexity derives from its restrained and multifaceted etiology (Dal Moro et al., 2005). Incidences of urinary stone are very ubiquitous worldwide amounting to an estimated 1500–2000 per million cases annually (Bartoletti et al., 2007) and increasing (Zampini et al., 2019). It is estimated that around 12% of residents of developed countries worldwide suffer from urolithiasis (Alelign and Petros, 2018). Whereas, a further 10% rise in this statistics is expected to occur within next 50 years due to global warming (Fakheri and Goldfarb, 2011). Urolithiasis is also a major contributor to an immensely large number of chronic kidney diseases and renal failure in India (Malhotra, 2008). In India, an estimated 12% of the population has urinary stone disease, with 50% of patients at high risk of renal dysfunction (Alelign and Petros, 2018; Cassell et al., 2020).

Recurrence associated with urolithiasis is yet another enigma

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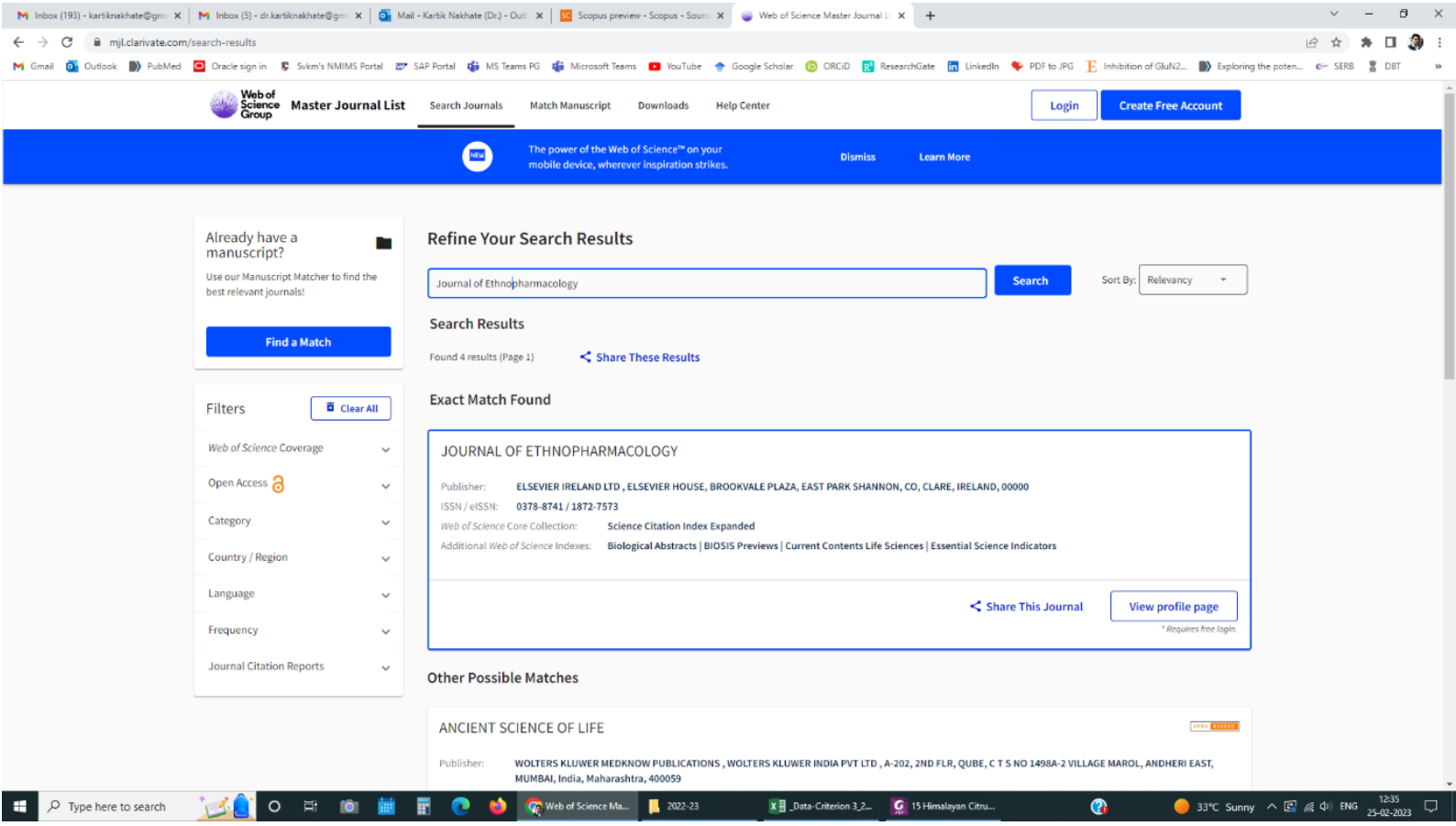
https://doi.org/10.1016/j.jep.2023.116157
Received 13 August 2022; Received in revised form 2 January 2023; Accepted 6 January 2023
Available online 13 January 2023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