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Original Article

Formulation and Evaluation of Phytosomes Loaded *Tinospora cordifolia* on Ethylene Glycol Induced Urolithiasis: An Experimental Study

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ABSTRACT

Background: *Tinospora cordifolia* is a renowned traditional medicinal herb known for its diverse therapeutic properties, including antioxidant, neuroprotective, and immunomodulatory effects. **Materials and Methods:** A hydroalcoholic extract of *T. cordifolia* was formulated into phytosomes and characterized for particle size, zeta potential, and polydispersity index. *In vitro* and *in vivo* antiurolithiatic activity were evaluated and compared with a standard drug. **Results:** Among the developed formulations, Batch 3 was identified as optimal, exhibiting a particle size of 158.1 nm, zeta potential of –28.15 mV, and a Polydispersity Index (PDI) of 0.3. *In vitro* analysis showed that the phytosome formulation dissolved 80% of calcium oxalate crystals, closely approaching the performance of the standard drug Cystone (86% dissolution). *In vivo* evaluation further demonstrated that both the crude extract and the phytosome formulation significantly improved altered biochemical markers such as urine output, pH, and levels of calcium, oxalate, uric acid, and magnesium. Histopathological examinations confirmed reduced renal crystal deposition and tissue damage in the phytosome-treated group, indicating enhanced protection against stone formation. **Conclusion:** Overall, the phytosome-based delivery of *Tinospora cordifolia* extract offers a promising and effective approach for the prevention and treatment of urolithiasis.

Keywords: Urolithiasis, *Tinospora cordifolia*, Phytosomes, Ethylene glycol.

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INTRODUCTION

Urolithiasis, characterized by the formation of crystalline mineral deposits within the urinary tract, remains a significant global health concern, affecting millions of individuals annually and demonstrating a high recurrence rate (Lang *et al.*, 2022). The condition is frequently associated with complications such as urinary obstruction, recurrent infections, renal inflammation, and gradual deterioration of renal function, thereby imposing a substantial clinical and socioeconomic burden (Shan, 2011). Although conventional therapeutic strategies, including citrate supplementation, thiazide diuretics, and urinary alkalinizers, are widely employed, their long-term utility is often compromised by adverse effects, limited patient compliance, and frequent relapse (Ellison & Loffing, 2009). Consequently, there is growing scientific interest in plant-derived therapeutics with a history of traditional use.

Tinospora cordifolia (Willd.) Miers, commonly known as Guduchi, is a well-recognized Ayurvedic "Rasayana" traditionally used in the management of fever, metabolic disorders, urinary tract ailments, and renal diseases (Rachana *et al.*, 2022). The plant is rich in bioactive phytoconstituents, including alkaloids, diterpenoid lactones, glycosides, and steroids, which contribute to its antioxidant, anti-inflammatory, immunomodulatory, and nephroprotective properties (Dhama *et al.*, 2016). These pharmacological attributes suggest its potential role in preventing and managing urinary stone disease (Pandey *et al.*, 2012). However, the therapeutic efficacy of conventional herbal extracts is often limited by poor solubility, low permeability, and reduced bioavailability (Dehelean *et al.*, 2021).

Phytosomes-phospholipid-based delivery systems have emerged as an effective strategy to enhance the stability, absorption, and bioavailability of phytoconstituents (Semalty *et al.*, 2010). In this context, the present study focuses on the development

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of a *Tinospora cordifolia*-loaded phytosomal formulation and its evaluation against ethylene glycol-induced urolithiasis, a well-established experimental model that closely mimics human calcium oxalate stone formation (Kumar *et al*., 2025; McMartin, 2009). Additionally, integrated *in silico* approaches, including molecular docking, ADME, and toxicity predictions, were employed to elucidate mechanistic interactions and support experimental findings (Pavithra, 2024; Gharge *et al*., 2025; Gudasi *et al*., 2025). In this context, the present study was designed to develop and characterize a *Tinospora cordifolia*-loaded phytosomal formulation and to evaluate its antiurolithiatic efficacy in an ethylene glycol-induced urolithiasis model.

MATERIALS AND METHODS

Preparation of Extract

The plant *Tinospora cordifolia* was collected from the local region of Gokak, District Belgaum. It was identified and authenticated by Shri B.M.K. Ayurveda Mahavidyalaya, Belagavi, and a specimen was deposited under CRF Code: CRF/AUTH/32/2023. The collected plant material was thoroughly cleaned, drained, cut into small pieces, and dried. For extraction, 1000 gm of the dried powdered material was macerated in 2.5 L of a hydroalcoholic solvent mixture (Ethanol: water, 70:30) for 7 days with occasional stirring. After maceration, the mixture was filtered, and the solvent was removed using a rotary evaporator to obtain the crude extract (Kambalyal *et al*., 2024; Desaipatti *et al*., 2025).

Phytochemical Screening

Qualitative phytochemical analysis was carried out on the extract to detect the presence of various bioactive constituents, including carbohydrates, alkaloids, flavonoids, saponins, sterols, and phenolic compounds (Patil *et al*., 2024).

Preparation and Characterization Phytosomes

Phytosomes were prepared using the thin-film hydration technique with slight modifications to ensure reproducibility and clarity. Briefly, the drug and cholesterol were accurately weighed and dissolved in methanol, while soy lecithin was dissolved separately in dichloromethane to obtain clear solutions. Both solutions were then combined in a round-bottom flask and subjected to solvent evaporation using a rotary evaporator maintained at 40°C with a rotation speed of 180 rpm under reduced pressure. This process resulted in the formation of a uniform thin lipid film on the inner wall of the flask. The dried film was further kept under vacuum to remove any residual organic solvents. Subsequently, the film was hydrated with an ethanol-water mixture (1:1, v/v) at 40°C for 1 hr with continuous gentle rotation to facilitate complete swelling and vesicle formation. The resulting dispersion was then sonicated for 30 min using a probe sonicator to reduce particle size and improve homogeneity of the phytosomal vesicles. The prepared phytosomal formulation was stored at appropriate conditions for further characterization studies, as described by Patil and Jalalpure (2024).

Animal Study Protocol

Adult male albino Wistar rats (180-250 g) were maintained in the animal house of KLE College of Pharmacy, Belagavi, under controlled environmental conditions (temperature 22-25°C, relative humidity 55-65%, and a 12 hr light-dark cycle) with free access to standard pellet diet and water. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC Reg. No. 221/Po/Re/S/2000/CPCSEA). Ethylene Glycol (EG)–induced urolithiasis was employed, and animals were randomly divided into six groups (n = 6) and treated for 28 days (Patel VB and Acharya N, 2020). Group I served as the normal group and received standard diet and drinking water, whereas Group II received 0.75% w/v EG in drinking water for 28 days to induce calculi formation. Group III was administered EG along with the standard drug Cystone (750 mg/kg) from day 15 to day 28. Groups IV and V received EG in combination with *Tinospora cordifolia* extract at doses of 250 and 500 mg/kg, respectively, from day 15 to day 28, while Group VI was treated with EG plus T. cordifolia phytosome (250 mg/kg) during the same period. Urine samples were collected using metabolic cages on day 14 and day 29 and analyzed for volume, pH, calcium, oxalate, magnesium, urea, and uric acid using diagnostic kits. Blood was collected on day 29 for serum biochemical analysis (Rashid *et al*, 2023). Animals were then sacrificed, kidneys were excised, homogenized for biochemical and antioxidant assays, and fixed in buffered formalin for histopathological evaluation of calcium oxalate crystal deposition.

RESULTS

Phytochemical Screening of Phytoconstituents

The qualitative phytochemical screening of *Tinospora cordifolia* revealed the presence of various bioactive constituents, indicating its rich therapeutic potential. The extract tested positive for phenolic compounds, terpenoids, alkaloids, sterols, flavonoids, tannins, carbohydrates, saponins, and glycosides. Notably, the absence of phytosterols was observed, suggesting selective distribution of sterol-type compounds in the plant.

Phytosome Characterization

The characterization data of the Formulations (F1-F4) show significant variation in particle size, zeta potential, Polydispersity Index (PDI), and Entrapment Efficiency (EE), indicating differences in stability and performance (Table 1). Formulation F3 exhibited the smallest particle size (158.1 nm), lowest PDI (0.3), and a moderate zeta potential of -28.15 mV, suggesting better homogeneity and physical stability (Figure 1). F1 had the largest particle size (521 nm) and the highest zeta potential (-51.3 mV), but a higher PDI (0.7), indicating a broader size distribution. F2

and F4 showed intermediate particle sizes (382 nm and 448 nm, respectively) with zeta potentials of -45.01 mV and -48.02 mV, and PDIs of 0.4 and 0.2, respectively. The entrapment efficiency was highest in F3 (82%), highlighting it as the most optimal formulation in terms of size, stability, and drug-loading capacity.

Morphology of Phytosome Vesicles

TEM analysis as presented in Figure 2 confirms the vesicle size measured by size analyzer and it confirms the particle size around 100-200 nm with spherical shape and uniform.

Urine parameters

The study evaluates the effect of *Tinospora cordifolia* extract and its phytosome formulations on urinary parameters in an animal model of urolithiasis. The disease control group exhibited significantly elevated levels of urinary calcium (10.37 mg), uric acid (4.42 mg), and oxalate (11.54 mg), alongside a marked reduction in magnesium (1.28 mg), indicating stone-forming conditions. Standard treatment effectively normalized all parameters close to the normal group values. Treatment 1 (extract alone) showed partial improvement, with reduced oxalate and slightly increased magnesium, but calcium and uric acid levels remained relatively high. Treatment 2 demonstrated better efficacy, significantly reducing calcium, uric acid, and oxalate levels, while increasing magnesium. The phytosome-treated group showed the most pronounced effect, bringing all parameters including calcium (3.96 mg), uric acid (2.91 mg), oxalate (8.39 mg), and magnesium (2.7 mg) closer to normal values, suggesting that phytosomal formulation of *T. cordifolia* enhances bioavailability and therapeutic efficacy in managing urolithiasis (Table 2).

Serum Parameters

The impact of *Tinospora cordifolia* extract and its phytosome formulation on serum biochemical markers was assessed to determine their renoprotective potential in urolithiasis. Disease control rats showed markedly elevated calcium, creatinine, urea, uric acid, and total protein levels, confirming severe renal impairment (Table 3). Cystone treatment significantly restored all parameters. The 250 mg/kg extract dose showed minimal improvement, whereas the 500 mg/kg dose produced a more substantial reduction. Notably, the 250 mg/kg phytosome formulation demonstrated highly significant normalization of all serum parameters, indicating superior bioavailability and enhanced therapeutic efficacy compared to the crude extract.

Antioxidant parameters

The study evaluated the effect of *Tinospora cordifolia* extract and its phytosome formulations on antioxidant enzyme levels in tissue homogenates by assessing Glutathione (GSH), Superoxide Dismutase (SOD), and Malondialdehyde (MDA). The disease control group exhibited significant oxidative stress, shown by markedly decreased GSH (5.71±0.13), reduced SOD (6.41±0.22), and elevated MDA (4.95±0.08) levels compared to the normal group, indicating impaired antioxidant defence (###p<0.001).

Table 1: Particle Size, Zeta Potential, PDI and Entrapment Efficacy.

Formulation	Particle size	Zeta potential	PDI	EE
F1	521	-51.3±51.3	0.7	F3=82%
F2	382	-45.01±45.01	0.4	
F3	158.1	-28.15±28.15	0.3	
F4	448	-48.02±48.02	0.2	

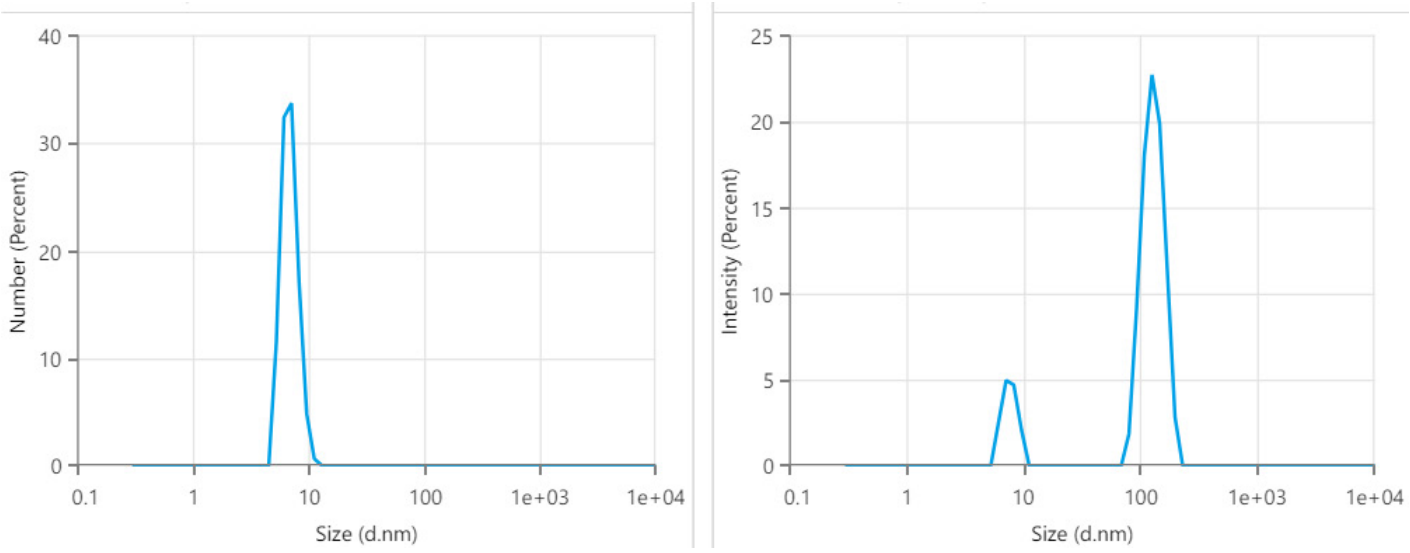

Figure 1: Particle size, zeta potential, PDI of phytosome.

Table 2: Effect of *Tinospora cordifolia* extract and phytosome on urinary parameter.

Groups	Urine parameters (mg/24 hr) (mean ± Sem)			
	Calcium	Uric acid	Oxalate	Magnesium
Normal	3.68±0.22	2.57±0.13	4.66±0.11	3.48±0.13
Disease control	10.37±0.13$^{###}$	4.42±0.18$^{###}$	11.54±0.13$^{###}$	1.28±0.04$^{###}$
Standard	3.8±0.06^{aaa}	2.83±0.21^{aaa}	8.1±0.2^{aaa}	3.02±0.12^{aaa}
TC (250mg/kg)	8.69±0.1^{ns}	3.32±0.23^{ns}	10.67±0.22^{a}	1.94±0.15^{aa}
TC (500mg/kg)	6.47±0.22^{a}	3.03±0.12^{aaa}	9.62±0.1^{aaa}	2.32±0.08^{aaa}
TCP (250mg/kg)	3.96±0.24^{aaa}	2.91±0.08^{aaa}	8.39±0.13^{aaa}	2.7±0.06^{aaa}

All the data were expressed as Mean ± SEM, where n=6.

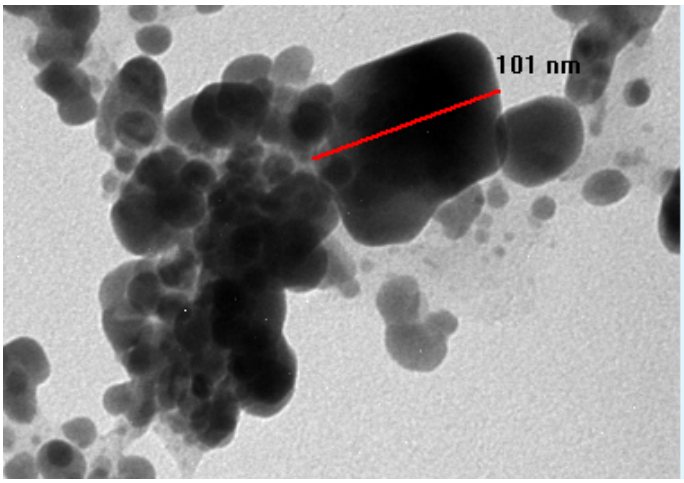

Figure 2: TEM analysis of phytosome.

Standard treatment significantly restored these markers near normal levels (Table 4). Among the treatment groups, Treatment 3 (phytosome 250 mg/kg) showed the most pronounced improvement with GSH (8.48±0.13), SOD (11.18±0.26), and MDA (2.62±0.16), suggesting strong antioxidant potential.

Histopathology of kidney

The kidney's microscopy section (Figure 3) demonstrated usual structure in the normal group, the presence of calcium oxalate crystals, severe damage to the glomeruli, medulla, interstitial spaces, tubules, and mononuclear cell infiltration in the disease control group, and major damage recovered in the kidney sections of the TC and TCP recipients, along with prevention of crystal deposition in the intratubular space. In the group receiving cystone treatment, there was no evidence of crystal deposition, and the kidney damage was nearly restored.

DISCUSSION

Kidney stone disease is an increasingly prevalent global health concern, affecting almost 12% of the population and rising steadily due to changing dietary patterns, lifestyle factors, and metabolic disturbances. Experimental models are essential for understanding lithogenesis and evaluating therapeutic interventions. Among these, the Ethylene Glycol (EG)-induced Calcium Oxalate (CaOx) rat model is considered one of the most reliable, as the resulting deposits closely mimic human renal calculi in mineral composition and ultrastructure (Patel & Acharya, 2020). The pathophysiology of urolithiasis is multifactorial, involving sequential physicochemical processes such as urinary supersaturation, nucleation, crystal growth, aggregation, and retention within renal tubules. Notably, rats do not spontaneously develop CaOx stones, making EG exposure a suitable method to induce lithogenesis for mechanistic and therapeutic studies.

EG-induced urolithiasis results primarily from its metabolic conversion to oxalic acid via nonspecific dehydrogenase enzymes, producing pronounced hyperoxaluria a key predisposing factor for CaOx crystallization (Amin *et al.*, 2015). EG also reduces urine output and elevates urinary calcium levels, promoting supersaturation and accelerating crystal nucleation and growth. These alterations closely resemble clinical urolithiasis, reinforcing the translational relevance of the model.

This study evaluated the antiurolithiatic potential of *Tinospora cordifolia* leaf extract through *in vitro* crystallization assays and *in vivo* investigations. *In vitro* assessments revealed that the extract effectively modulated early crystallization events. Supersaturation of calcium and oxalate ions is the primary driver of CaOx crystal formation, and agents capable of reducing nucleation or inhibiting aggregation can significantly prevent or delay lithiasis (Sheng *et al.*, 2005). Among the CaOx polymorphs, Calcium Oxalate Monohydrate (COM) is more stable and pathogenic due to its greater affinity for renal epithelial adhesion and higher tendency to aggregate compared with Calcium Oxalate Dihydrate (COD) (Wesson *et al.*, 1998).

The *T. cordifolia* hydroalcoholic extract demonstrated moderate but meaningful inhibition of CaOx crystallization, achieving 71% inhibition relative to the standard drug Cystone. Titrimetric analysis further indicated CaOx dissolution of 0.71 mg, supporting its inhibitory potential. The concentration-dependent reduction in crystal size and number suggests interference with nucleation, growth, and aggregation. These effects are likely attributable to the alkaloids, phenolics, and terpenoids in *T. cordifolia*, which may chelate calcium ions, modify crystal morphology, and

Table 3: Effect of *Tinospora cordifolia* extract and phytosome on serum parameter.

Groups	Serum parameters (mg/dl) (Mean ± Sem)				
	Calcium	Creatinine	Urea	Uric acid	Total protein
Normal	10.25±0.06	0.76±0.05	15.07±0.22	6.38±0.12	6.82±0.24
Disease control	14.22±0.11$^{###}$	4.08±0.03$^{###}$	28.2±0.17$^{###}$	11.5±0.12$^{###}$	11.61±0.38$^{###}$
Standard (750mg/kg)	11.01±0.09 ^{aaa}	1.55±0.07 ^{aaa}	18.87±0.19^{aaa}	7.53±0.17 ^{aaa}	8.41±0.28 ^{aaa}
TC (250mg/kg)	14.04±0.3 ^{ns}	3.77±0.08 ^{ns}	26.2±0.96 ^{a}	10.46±0.24^{aa}	11.01±0.11 ^{ns}
TC (500mg/kg)	12.6±0.2^{aaa}	2.6±0.08^{aaa}	23.2±0.27^{aaa}	8.36±0.27^{aaa}	10.03±0.24^{aa}
TCP (250mg/kg)	11.85±0.24^{aaa}	2.23±0.31 ^{aaa}	20.93±0.13 ^{aaa}	7.2±0.19^{aaa}	9.42±0.21^{aaa}

All the data were expressed as Mean ± SEM, where *n*=6.

Table 4: Effect of *Tinospora cordifolia* Extract and Phytosome on Antioxidant Enzyme in Tissue Homogenate.

Groups	GSH	SOD	MDA
Normal	9.16±0.12	12.48±0.19	1.59±0.17
Disease Control	5.71±0.13###	6.41±0.22###	4.95±0.08###
Standard	8.76±0.15AAA	11.83±0.37 AAA	1.69±0.07 AAA
TC (250mg/kg)	6.45±0.13AA	7.78±0.16 AAA	3.8±0.08 AAA
TC (500mg/kg)	7.56±0.14AAA	9.74±0.29 AAA	2.88±0.12 AAA
TCP (250mg/kg)	8.48±0.13AAA	11.18±0.26 AAA	2.62±0.16 AAA

All the data were expressed as Mean ± SEM, where *n*=6.

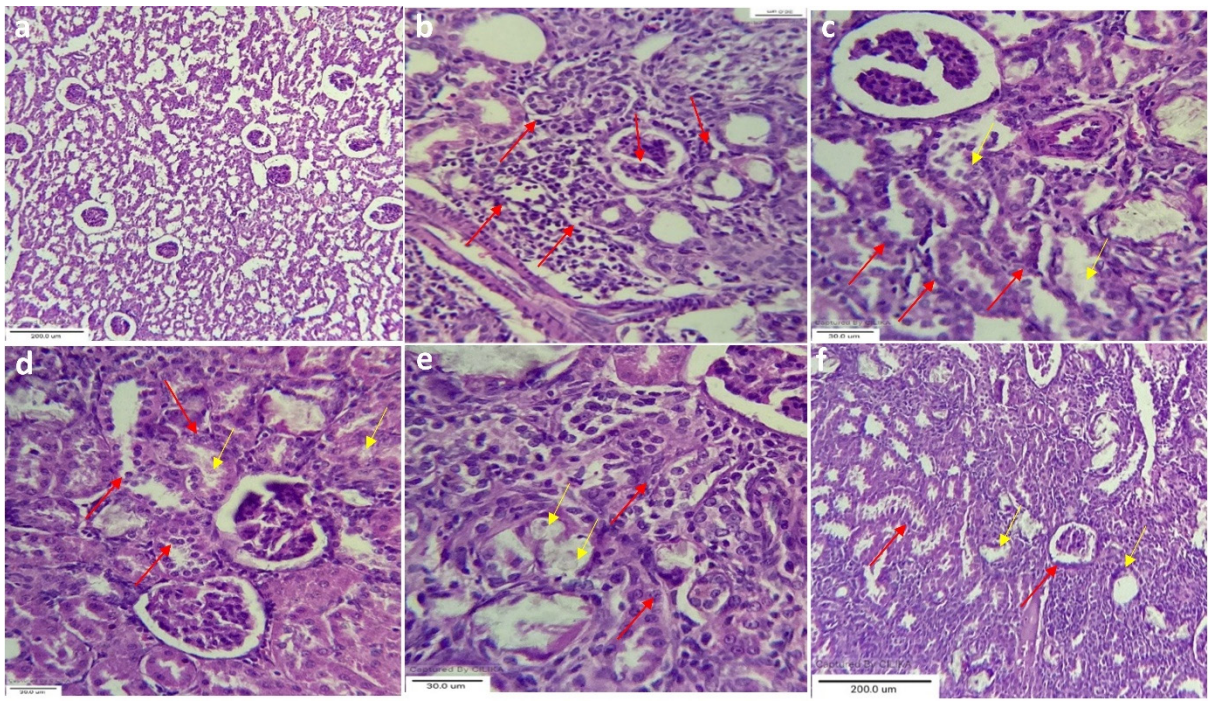

Figure 3: Microphotographs of Histopathology of kidney (a) Norm al group, (b) Disease control group showed crystal deposition having large size, (c) Standard group (Cystone (750 mg/kg) treated), (d) Treatment group I (250 mg/kg TC), (e) Treatment group II (500 mg/kg TC) and (F)Treatment group III (250 mg/kg TCP).

prevent aggregation or epithelial adhesion (Betanabhatla *et al.*, 2009). Smaller crystals are more easily excreted, reducing the risk of retention and stone maturation.

In vivo results further confirmed the protective effects of *T. cordifolia*. EG-induced rats exhibited classic indicators of lithogenesis: decreased urinary pH, elevated urinary oxalate, calcium, and uric acid, and reduced magnesium levels. Treatment with the extract significantly normalized these parameters. Increased urinary pH enhances CaOx solubility, while restoration of magnesium is particularly beneficial, as magnesium forms soluble complexes with oxalate, reducing free oxalate available for crystallization (Sridharan *et al.*, 2016).

Histopathological evaluation provided strong corroborative evidence. Disease control animals showed extensive renal tubular CaOx deposits and tissue damage, whereas *T. cordifolia*-treated groups exhibited markedly reduced crystal deposition and preserved renal structure. Oxidative stress, a major contributor to EG-induced renal injury, was also ameliorated. Elevated Malondialdehyde (MDA) levels and reduced antioxidant enzymes such as catalase and Superoxide Dismutase (SOD) in disease controls were significantly improved following treatment, highlighting the extract's antioxidant and anti-inflammatory actions attributed to its phenolic and steroidal constituents (Lee *et al.*, 2012).

CONCLUSION

The results of this investigation clearly show that the TC leaf extract has antiurolithiatic ability against CaOx urolithiasis both *in vitro* and *in vivo*. We can therefore conclude that TC has antiurolithiatic activity in EG-induced urolithiasis by increasing inhibitors such as magnesium and inhibiting other promoters in blood, urine, and kidney tissue, such as calcium, oxalate, and phosphate. Moreover, TC possesses a strong diuretic effect that can aid in eliminating promoters from the urine and accelerate the breakdown of calcium oxalate stones, hence halting the production of new stones. In rats subjected to crystal formation, administration of TC extract improves renal function while preventing excessive kidney stone development. The current research highlights that TC may have therapeutic efficacy and is helpful in the treatment and prevention of renal stone development. Thus, more clinical research is desperately needed to confirm TC's potential as a preventive and therapeutic intervention for kidney stone disease patients.

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ABBREVIATIONS

COD: Calcium dihydrate; **COM:** Calcium monohydrate; **EG:** Ethylene Glycol; **TC:** *Tinospora cordifolia*; **TCP:** *Tinospora cordifolia* Phytosome.

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