RESEARCH PAPER

Repurposing of Marketed Drugs for Anti-Urolithiatic Activity by In Silico, Network Pharmacology and In Vitro Methods

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ABSTRACT
The present study aimed to repurpose marketed drugs for anti-urolithiatic activity using integrated in silico, network pharmacology, molecular simulation, nanoparticle formulation, and in vitro approaches. Marketed drugs were selected based on their mechanism of action and structural characteristics. The selected compounds were evaluated using SwissTarget Prediction, Molinspiration, toxicity prediction tools, and molecular docking through AutoDock Vina. Epigallocatechin gallate (EGCG) was identified as the most promising candidate and further investigated using network pharmacology to determine its potential targets, with Schrödinger software employed to identify the most active target. EGCG-loaded chitosan nanoparticles (CNPs) were developed to enhance solubility and encapsulation efficiency. The nanoparticles were characterized using Zeta sizer, SEM, FTIR, and DSC analysis. Anti-urolithiatic activity was assessed through in vitro cell line assays and Nucleation, Aggregation, Crystallization methods . EGCG exhibited favorable docking scores against 3KS3 (carbonic anhydrase-2), 2ETE (oxalate oxidase-1), and 2RDT (human glycolate oxidase). The binding stability was further confirmed from molecular docking and molecular dynamics simulation studies on 1UNQ, 7AOT and 5GJK. Both EGCG and EGCG-CNP demonstrated significant anti-urolithiatic activity compared to vitamin E. Overall, the findings suggest that EGCG and its nanoparticle formulation possess promising anti-urolithiatic potential validated through in silico and in vitro studies.

Keywords: Network pharmacology, Epigallocatechin gallate, Molecular docking, Repurposing, MD simulation and in vitro urolithiasis.

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1. INTRODUCTION

Around 10-15% of the world's population suffer from uric lithiasis, in which the patient develops lith in his kidneys, ureters or bladder, with a prevalence of calcium oxalate in around 70-80% of the patients. Formation of calculi occurs through urinary supersaturation, nucleation, growth and retention of crystals, and it is usually accompanied by metabolic disorders, oxidative stress and inflammation. [3,4]. Despite progress in surgical and drug-based treatment methods, the rate of recurrence is still quite high, emphasizing the importance of using new therapies that can target the molecular pathway involved in its formation. Drug repurposing has become a promising technique due to its low cost; it has been validated with the help of several computational techniques, including molecular docking and pharmacological network analysis. [5,6]. The objectives of the current research work include rational drug repurposing of selected drugs for anti urolithiatic activity through virtual screening against target proteins responsible for calcium oxalate crystal formation and inflammatory pathways in kidneys, and then formulating these selected drugs in chitosan nanoparticles. [6,7]. The hypothesis is that the repurposing of drugs via an advanced chitosan nano delivery system will result in effective inhibition of crystals along with oxidative and inflammatory damage in the kidneys. This approach based on the combined use of computational tools and nanotechnology holds significant promise for the development of a novel treatment approach for urolithiasis. [2,8].

2. MATERIALS AND METHODS

About 40 compounds have been chosen and analyzed using Swiss Target Prediction and Auto Dock vina approaches in that the following compounds have been chosen according to their mechanism and structural formula. This research involved computational analysis, formulation, physicochemical characterizations, and in vitro biological studies of anti-urolithiatic activity of EGCG and CNP formulations.

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2.*1 In Silico* and Network Pharmacology Studies

The compound and the possible molecular targets were determined by means of literature search and online databases such as DrugBank, PLATO, and SwissTargetPrediction. The urolithiasis-related genes were collected from GeneCards, and the shared targets were determined using Venny 2.1.[9] PPI analysis was carried out in the STRING database, and functional enrichment analysis in ShinyGO[10,11]. Compound-target and PPI network construction and analysis were carried out in Cytoscape 3.10.2, and hub genes were selected on the basis of network topology[12]. Prediction of toxicity was made using ProTox-II, while pharmacokinetics and drug-like characteristics were evaluated using Swiss ADME and Molinspiration. Prediction of toxicity was made using ProTox-II.

2.2 Docking and Molecular Dynamics Simulation Studies

Molecular docking simulation was done by using AutoDock Vina and Schrödinger Glide to determine the binding affinity of EGCG on selected proteins associated with urolithiasis (PDB IDs: 1UNQ, 7AOT, and 5GJK). Docking results with better binding energy were selected for validation by carrying out 10 ns molecular dynamics simulations by using GROMACS with GROMOS43a1 force field.

2.3 Preparation of EGCG Chitosan Nanoparticles, Characterization and Stability studies

The ionic gelation technique was used to make EGCG loaded chitosan nanoparticles with the assistance of chitosan and STPP[12,13]. The nanoparticle solution was centrifuged and lyophilized in order to make nanoparticles. The nanoparticles thus prepared were studied for size analysis, SEM, interaction between drug and polymer by FTIR, and thermal behavior by DSC [14,15].

2.4 In Vitro Cell Viability Study

Cytoprotective effect of EGCG and EGCG-containing chitosan nanoparticles was determined by MTT assay for HEK-293 (Human Embryonic Kidney) cells. The cells were cultivated in DMEM with fetal bovine serum and antibiotics at the optimal conditions of temperature (37°C) and CO_2 content (5%). For generation of urolithiasis-like injury, the culture of cells was exposed to 20 µM sodium oxalate and further incubated with different concentrations of EGCG and EGCG-containing nanoparticles (12.5-200 µg/ml). The viability of cells was determined by MTT assay after 24 h of incubation with the drugs and measured by the optical density reading at 570 nm. Cell viability was calculated as:

$$\text{Percentage Cell Viability} = A_{treated} / A_{control} \times 100$$

2.5. In Vitro Screening for Anti-Urolithiatic Activity

In vitro urolithiatic activity of the test samples was assessed by in vitro nucleation, aggregation and crystal growth inhibition assays. The samples were then incubated in calcium oxalate crystal-forming solutions and in preformed crystals of calcium oxalate monohydrate, at various concentrations. The absorbance was measured after incubation at 620 nm and the percentage of the inhibition of crystal formation, crystal aggregation and crystal growth was calculated to assess the anti-urolithiatic activity[16].

3. RESULTS

3.1. *Insilico* studies

3.1.1. Swiss Targeting

Structure-based and mechanism-based compounds were screened using Swiss Target Prediction to identify potential molecular targets associated with urolithiasis, and compounds exhibiting favorable target profiles, including EGCG, were selected for further computational and experimental investigations.

3.1.2. Auto Dock Vina

Based on enzyme target, 3KS3(carbonic anhydrase - 2),2ETE(Oxalate oxidase-1),2RDT (Human Glycolate oxidase) enzymes are selected. The results are mentioned in the (Table 1) and docking studies performed in that EGCG showed good binding affinity.

3.2. Integrated Network and Pathway Analysis

3.2.1. Identification of Probable Biological Targets for Selected Drug

The Pub Chem entry for epigallocatechin gallate was selected as the canonical source for the target prediction that followed. By using a probability larger than "Zero," Swiss target prediction generated 102 targets.

3.2.2. Identification of Known Therapeutic Targets for Urolithiasis

Using the term Urolithiasis, gene cards generated 666 therapeutic targets with a score limit of ≥ 3.66. OMIM generated 666 therapeutic targets with their phenotypic MIM numbers, which were then translated into uniport gene symbols using uniport (Table 2).

3.2.3. Identification of Potential Therapeutic Targets of EGCG for Anti-Urolithiasis activity

A Venn diagram was created between the 666 therapeutic targets of urolithiasis and the 102 likely biological targets of EGCG, yielding 13 and 9 promising targets that were utilized for additional investigation. The above mentioned are the intersection analysis between active constituents and disease related targets for the EGCG.

3.2.4. Protein Interaction Network Analysis Using STRING

Proteins were then retrieved from the STRING database and the PPI network was constructed and analyzed using the Cytoscape software to find key hub proteins based on network topology (Figure 1). The topological properties of the proteins in the PPI network were used to select hub proteins, including the degree, betweenness centrality and closeness centrality.

3.2.5. Gene Ontology and Pathway Enrichment Analysis

To determine the functions and pathways of the target genes, enrichment analysis with respect to Gene Ontology

(GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis were performed on the target genes using ShinyGO tool (Figures 2,3,4,5,6). The enriched biological processes, molecular functions, cellular components and signalling pathways were calculated by the significance of bubble charts. Furthermore, the association between the bioactive compound, target protein and biological pathway involved in urolithiasis were illustrated using the interaction network generated via Cytoscape (compound–target-pathway analysis).

3.2.6. Development of the Compound–Target–Pathway Interaction Network

A compound–target–pathway interaction network was constructed and analyzed using Cytoscape to visualize the relationships among the bioactive compound, predicted targets, and significantly enriched pathways, and to identify key hub targets based on network topological parameters (Figures 7 and 8; Table 3). The prioritized hub targets identified through network pharmacology analysis were subsequently selected for molecular docking studies to evaluate their potential interactions with the bioactive compound.

3.3. Molecular docking

The selected bioactive compound binding affinity and interaction patterns were evaluated by molecular docking studies with the prioritized hub target proteins and the docking scores and interaction profile were compared with that of the corresponding standard ligand. (Tables 1 and 4; Figures 9,10,11). The results demonstrated favorable binding affinities and stable molecular interactions with the selected target proteins, supporting the potential therapeutic role of the bioactive compound against urolithiasis. Based on Glide score, EGCG shows good binding affinity towards 1UNQ, 7AOT, 5GJK.

3.4. MD Simulations

EGCG showed good activity so that its binding affinity towards2ETE and 1UNQ can be measuredby MD Simulation study (Figure 12).We observed that the substance EGCG interact steadily with 2ETE-Oxalate oxidase and 1UNQ (Estrogen receptor alpha). Further the drug pharmacokinetic parameters and physicochemical properties are checked by Swiss ADME (Table 5 & Figure 13) and Molinspiration studies.

3.5. Swiss ADME for EGCG

3.5.1. Molinspiration for EGCG

The Study performed to find the physicochemical properties.

3.5.2. Toxicity Predicition

The projected toxicity class for the compounds EGCG (Table 6 & Figure 14).

3.6. Stability studies and Characterization of nanoparticles

FTIR analysis revealed the characteristic functional groups of EGCG, including **–OH stretching at 3433 cm^{-1}, ester C=O stretching at 1694 cm^{-1}, and aromatic peaks at 1611, 1534, and 1461 cm^{-1}**, which were retained in the EGCG-loaded chitosan nanoparticles, indicating successful encapsulation without significant chemical interaction.

DSC analysis showed a characteristic endothermic peak of pure EGCG at **227.47 °C**, while the nanoparticle formulation exhibited a slight shift in the thermal peak, confirming good drug–polymer compatibility and successful incorporation of EGCG into the chitosan matrix without chemical modification.

SEM analysis was performed to evaluate the size of the nanoparticles of EGCG and the size of the nanoparticles observed in the range of 16nm – 90nm.

Particle size analysis using the **HORIBA SZ-100 nanoparticle analyzer** demonstrated that the prepared chitosan nanoparticles possessed a size range of **1–200 nm**, confirming successful nanoscale formulation.

Zeta potential analysis showed that the nanoparticles exhibited a positive surface charge in the range of **+13 to +80 mV**, indicating good colloidal stability of the chitosan nanoparticle formulation (Tables 7; Figure 15).

3.7. Invitro Cellular Studies

We have chosen epigallocatechin gallate (EGCG) and EGCG-CNP against sodium oxalate (SO)-induced urolithiasis in HEK293 cells *in vitro* based on our prior *in silico* finding. With increases in EGCG and EGCG CNP concentration, a steady decrease in absorbance was seen. In the 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg EGCG groups, the percentage inhibition was 27.18, 27.06, 28.28, 30.57, and 36.03, and in the 12.5 µg, 25 µg, 50 µg, 100 µg, and 200 µg EGCG CNP groups, the percentage inhibition was 15.82, 23.87, 29.99, 38.44, 41.75, 76.28 respectively (Table 8). The concentration-related rise in EGCG ability to prevent the formation of sodium oxalate crystals was lower than that of vitamin E (m) (Figures 16,17).

3.8 Invitro anti-urolithiatic activity

Nucleation Assay:

EGCG exhibited a concentration-dependent increase in nucleation inhibition, increasing from **125% at 50 µg/mL** to **180% at 250 µg/mL**. In comparison, Cystone showed inhibition from **35% to 80%** across the same concentration range, indicating greater nucleation inhibitory activity of EGCG (Figure 18).

Aggregation Assay:

Both EGCG and Cystone showed dose-dependent inhibition of crystal aggregation. EGCG increased from **42% at 50 µg/mL** to **72% at 250 µg/mL**, while Cystone increased from **45% to 70%**, demonstrating comparable inhibitory effects at higher concentrations (Figure 18).

Crystallization Assay:

EGCG inhibited crystal growth by **38%, 55%, and 70%** at **100, 500, and 1000 µg/mL**, respectively. Cystone

showed **45%, 60%, and 78%** inhibition at the corresponding concentrations, indicating slightly higher crystallization inhibitory activity (Figure 18).

Overall:
EGCG demonstrated superior nucleation inhibitory activity and comparable aggregation and crystallization inhibitory effects to Cystone, confirming its significant antiurolithiatic potential against calcium oxalate crystal formation.

4. DISCUSSIONS

In the present study Epigallocatechin gallate (EGCG) nanoparticles prepared and characterized by Zeta sizer. EGCG nanoparticles are tested for in vitro cell line methods in this study EGCG nanoparticles were showed good cell protection activity which is related to anti urolithiatic activity. Repurposing of EGCG for anti urolithiatic activity confirmed by docking study in that compared to all repurposed drugs EGCG showed good binding affinity towards 3KS3, 2ETE and 2RDT. By Network Pharmacology study ESR1 gene and CA2 gene are specifically find out the GO and KEGG analysis. These 2 genes are indirectly and directly responsible for oxalate oxidase, carbonic anhydrase mediated Anti-urolithiatic activity. So, that CA2 target 3KS3 and 2ETE are selected for autodocking study in that EGCG (-7.7, -7.9) showed good binding affinity. By Network pharmacology study urolithiasis genes found in that estrogen related protein 1UNQ and 2ETE are specific targets for EGCG. MD simulation studies showed good binding affinity toward these two proteins. EGCG selected for nanoparticle preparation stability studies performed by Zeta-sizer, SEM analysis and these compounds studied on cell line (HEK-293 cells) activity so in that study nanoparticle showed good % inhibition of cell viability. EGCG also showed good inhibitory activity against Nucleation, Aggregation, Crystallization methods compared to standard cystone. From the above studies, we found that EGCG is potent molecule for the Anti-urolithiatic activity. Then this molecule is studied for the physicochemical and pharmacokinetic profiles by Molinspiration and SWISS ADME. This study evaluated that EGCG is the good molecule following Lipinski rule of five and good bioavailability with less toxicity.

5 .CONCLUSION

EGCG particularly when formulated as nanoparticles, is a highly potent candidate for anti-urolithiatic therapy. By utilizing Network Pharmacology to identify ESR1 and CA2 as key regulatory genes, the research established a clear mechanistic link between EGCG the modulation of enzymes like oxalate oxidase and carbonic anhydrase. Molecular docking and MD simulations confirmed that EGCG maintains superior binding stability with targets 3KS3 and 2ETE compared to traditional drugs like Doxycycline. The EGCG-loaded nanoparticles exhibited good stability during storage, with minimal changes in particle size, polydispersity index, zeta potential, entrapment efficiency, and drug content. No significant aggregation or degradation was observed, and the formulation retained its antioxidant activity, indicating that the nanoparticles are stable and suitable for pharmaceutical applications. Furthermore, *in vitro* testing on HEK-293 cells proved that the nanoparticle delivery system significantly enhances cell protection and viability inhibition. Coupled with a favorable Swiss ADME profile that confirms Lipinski's Rule compliance and high bioavailability, EGCG emerges as a safe and effective repurposed molecule for the prevention and treatment of urolithiasis.

6. ACKNOWLEDGEMENT

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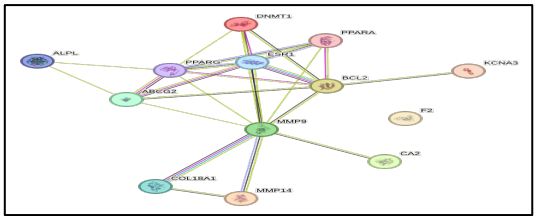

Figure 1. The STRING PPI network of Potential targets for EGCG

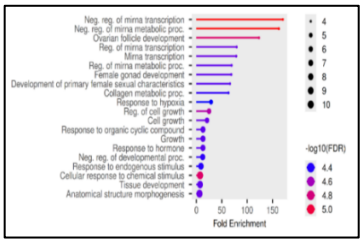

Figure 2. Biological process

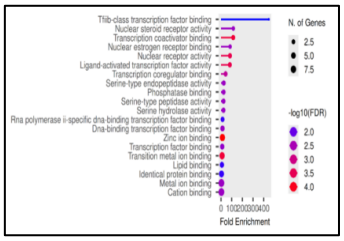

Figure 3. Molecular Function

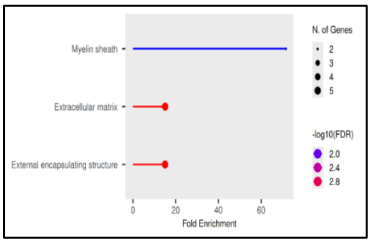

Figure 4. Cellular composition

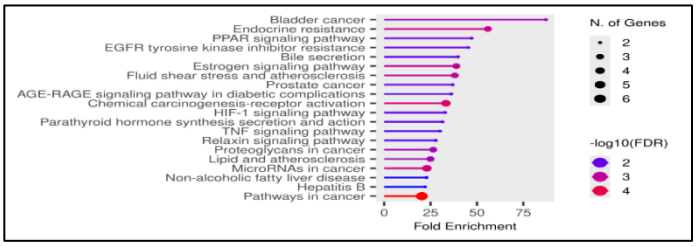

Figure 5. KEGG pathway enrichment Analysis for EGCG

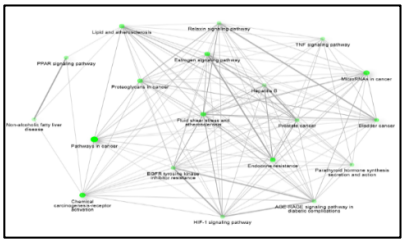

Figure 6. KEGG pathway (EGCG)

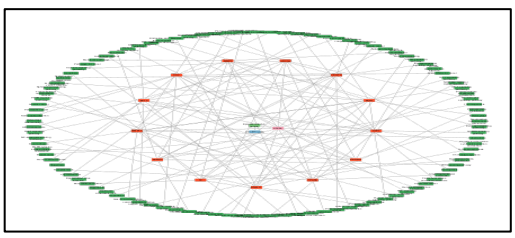

Figure 7. Potential Target-Pathway network

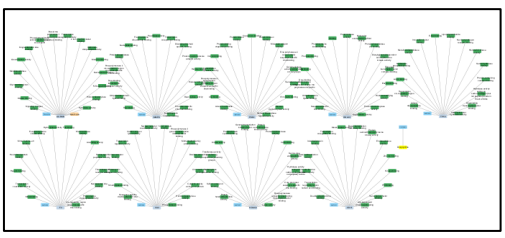

Figure 8. Potential Target-Pathway network

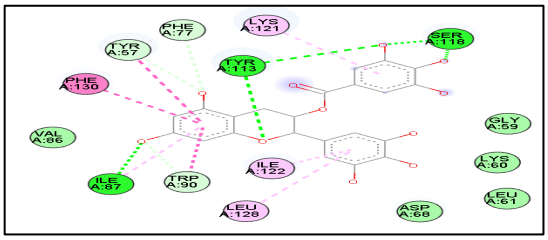

Figure 9.2D images with 7AOT

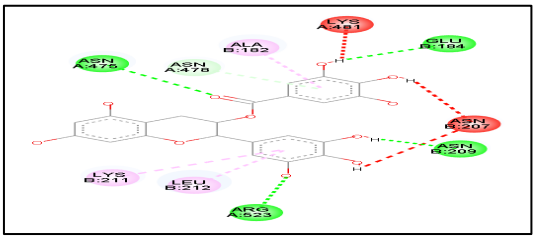

Figure 10. 2D image with 5GJK

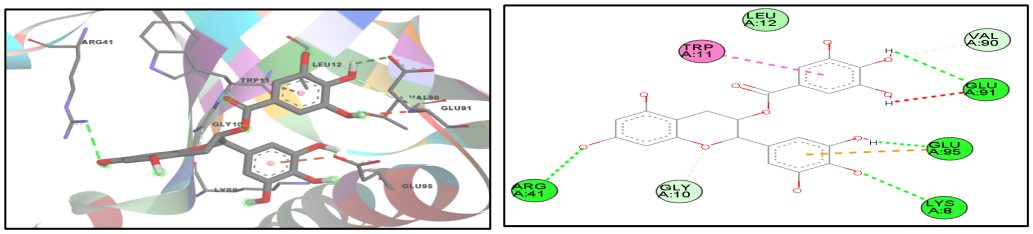

Figure11. 3D and 2D EGCG shows good interactions with 1UNQ

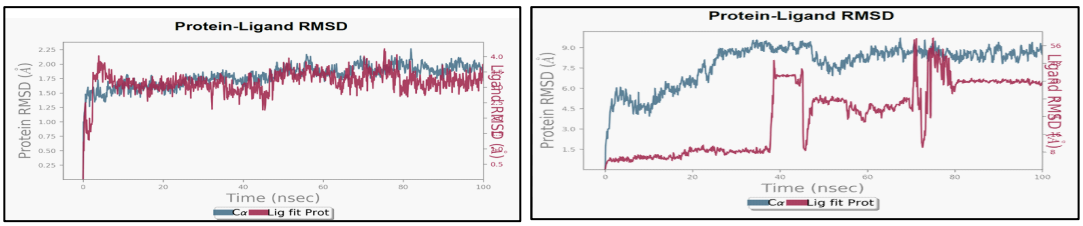

Figure12. RMSD of EGCG during molecular dynamic simulation in 2ETE and 1UNQ.

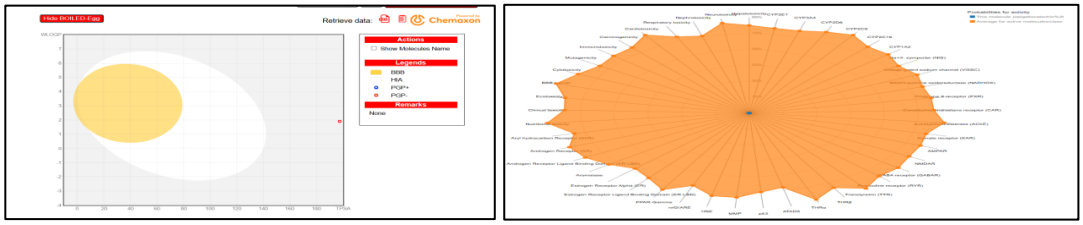

Figure 13. Boiled egg model of EGCG

Figure 14. Toxicity radar chart of EGCG

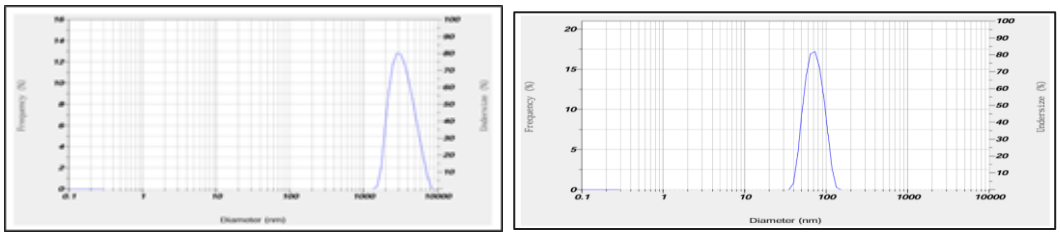

Figure 15. Size distribution curve of EGCG and EGCG-loaded CNP

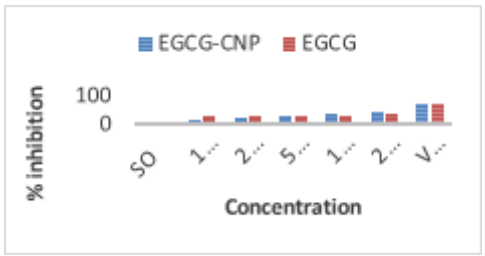

Figure 16. % inhibition of EGCG

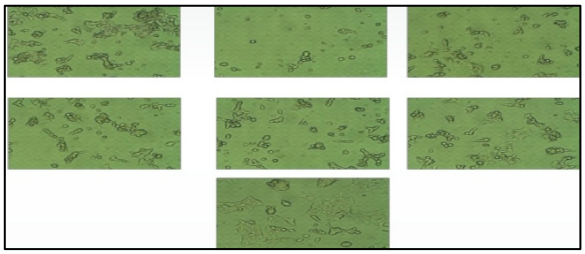

Figure 17. Images represent A) Sod oxalate- 8mM (SO), &EGCG-CNP on cell viability B) SO + EGCG-12.5ug, C) SO + EGCG - 25ug, D) SO + EGCG -50ug, E) SO+ EGCG -100ug, F) SO + EGCG - 200ug and G) SO + Vitamin-E 15uM.

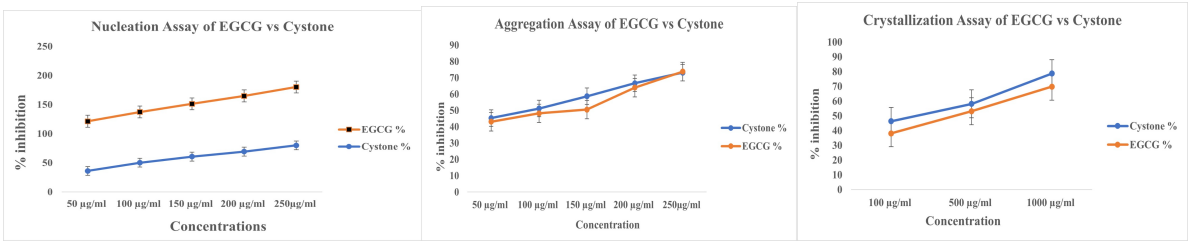

Figure 18. Evaluation of the EGCG on a) Nucleation assay, b) Aggregation assay, and c) Crystallization assay

Table 1. Molecular docking studies of selected ligands by AutoDock vina

S. No	Ligands	Proteins		
		3KS3	2RDT	2ETE
1.	Epigallocatechin gallate	**-7.9**	-5.9	**-7.7**
2.	Doxycycline	**-8.0**	-6.2	**-7.0**
3.	Probenecid	-6.4	-5.5	-5.5
4.	Umbelliferone	-7.3	-5.8	-5.6
5.	Gallic acid	-6.6	-5.5	-5.8
6.	Acetazolamide	-7.0	-5.6	-5.5
7.	Hydrochlorothiazide	-7.4	-5.6	-5.6
8.	Brinzolamide	-6.4	-4.5	-5.1
9.	Ethoxzolamide	-6.4	-4.4	-6.0
10.	Acetohydroxamic acid	-4.4	-3.7	-5.5

Table 2. Uniport ID and respective gene symbols of potential targets of EGCG against Urolithiasis

S.NO	UNIPORT ID for EGCG	GENE SYMBOL for EGCG
1	P26358	DNMT1
2	P50281	MMP14
3	P10415	BCL2
4	P00918	CA2
5	P14780	MMP9
6	Q9UNQ0	ABCG2
7	P15692	VEGFA
8	P03372	ESR1
9	P05186	ALPL
10	P37231	PPARG
11	Q07869	PPARA
12	P22001	KCNA3
13	P00734	F2

Table 3. Compound-Target-Pathway Network analysis report showing Top 10 hub protein targets for EGCG

S.NO	Gene Symbol for EGCG	Gene Name for EGCG
1	DNMT1	DNA (Cytosine-5)-Methyltransferase 1
2	ABCG2	ATP-Binding Cassette Sub-Family G Member 2
3	BCL2	B-Cell Lymphoma 2
4	ESR1	Estrogen Receptor 1
5	PPARG	Peroxisome Proliferator-Activated Receptor Gamma
6	MMP9	Matrix Metallopeptidase 9
7	MMP14	Matrix Metallopeptidase 14
8	COL18A1	Collagen Type XVIII Alpha 1 Chain
9	ALPL	Alkaline Phosphatase, Liver/Bone/Kidney
10	PPARA	Peroxisome Proliferator-Activated Receptor Alpha

Table 4. Molecular docking studies of EGCG by Schrodinger

Ligand	Protein	Electrostatic	H-Bond Interactions	Hydrophobic	Glide Score (Kcal/mol)
Epigallocatechin gallate (EGCG)	7AOT	--	ILE87, TYR113, SER118, TYR57, PHE77, TRP90	TRP90	-7.9
	5GJK	--	ASN475, ARG523, GLU184, ASN209, ASN478	ALA182, LYS211	-7.6
	1UNQ	GLU95	LYS8, ARG41, GLU91, GLU95, GLY10, VAL90	TRP11, LEU12	-7.2

Table 5. Swiss ADME data of EGCG

Properties	Observations	Values
Lipophilicity	mlog P	1.53
Pharmacokinetics	GI	Low
	BBB	No
	p- gp substrate	No
	CYP2D6	No
	Log Kp (skin permeation)	-8.27
Drug likeness	Lipinski	N0; 2 violations
	BA score	0.17
Leadlikeness	No, 1 violation	
Water solubility	-4.91	

Table 6. Toxicity prediction of EGCG

Target	EGCG	
	Prediction	Probability
Hepatotoxicity	Inactive	0.70
Carcinogenicity	Inactive	0.54
Mutagenicity	Inactive	0.70
Cytotoxicity	Inactive	0.82

Table 7.Observations of the size & Zeta potential of nanoparticles

S. No	Compound	Mean size range (nm)	Zeta Potential(mv)
1	EGCG	3322.1	12.3mv
2	EGCG-CNP	68.5	46.7mv

Table 8. Dose dependent efficacy of EGCG & EGCG-CNP in human embryonic kidney cells (HEK293)- MTT

Groups	EGCG	Groups	EGCG-CNP
	% Inhibition		% Inhibition
Sod oxalate-8mM (SO)	04.24	Sod oxalate-8mM (SO)	4.24

SO + EGCG-12.5ug	27.18	SO + EGCG-CNP-12.5ug	15.82
SO + EGCG-25ug	27.06	SO + EGCG-CNP-25ug	23.87
SO + EGCG-50ug	28.28	SO + EGCG-CNP -50ug	29.99
SO + EGCG 100ug	30.57	SO + EGCG-CNP 100ug	38.44
SO + EGCG 200ug	36.03	SO + EGCG-CNP 200ug	41.75
SO + Vitamin-E 15uM	76.28	SO + Vitamin-E 15uM	76.28

Values represent mean ± SD of absorbance.