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Molecular Docking Analysis for the Identification of Bioactive Compounds Against Urolithiasis (Hyperoxaluria)

R. RAMKUMAR[1] and S. K. PERIYASAMY[2*]

[12*]Post Graduate Research, Department of Chemistry, Jamal Mohamed College (Autonomous), Affiliated to Bharathidasan University, Tiruchirappalli-620020, Tamilnadu, India.
*Corresponding author E-mail: nctperiya85@gmail.com

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ABSTRACT

Docking is a term used for computational plans that undertaking to observe the best associating between two particles: a receptor and a ligand. Atomic docking is perhaps the most tremendous piece of the time included strategies in structure-based medicine game plan, by temperance of its ability to expect the keeping assortment of little molecule ligands to the genuine objective limiting site. Nuclear docking is the cycle that put particles for appropriate plans to connect with a receptor. Sub-nuclear docking is a brand name cycle which occurs inside the space of seconds in a cell. Depiction of the restricting behavior expects an essential part in sensible game-plan of meds correspondingly as to explain head biochemical cycles. Calcium oxalate monohydrate is the essential constituent of most of renal stones. Osteopontin, an aspartic corrosive rich urinary protein, and citrate, a lot more modest atom, are intense inhibitors of calcium oxalate monohydrate crystallization at levels present in typical pee. Present thoughts of the gig of site-express coordinated efforts in crystallization got from examinations of biomineralization are surveyed to give a setting to understanding guideline of COM improvement at a nuclear level. In this paper, the nuclear docking of *In vitro* calcium oxalate monohydrate tests with their cooperation are discussed and separated.

Keywords: *In vitro* Calcium, *Trachyspermum ammi*, Calcium oxalate, Inflammation.

INTRODUCTION

Trachyspermum ammi-otherwise called ajowan caraway, thymol seeds, minister's weed, or carom is a yearly spice in the family Apiaceae. Both the leaves and the seed-like natural product of the plant are consumed by people. In the field of sub-nuclear showing, docking is a strategy which predicts the leaned toward heading of one molecule to a resulting when bound to each other to outline a consistent capricious. Hyperoxaluria that is, raised urinary release of the metabolic completed outcome oxalate can add to kidney stone turn of events and other clinical issues. The normal upper level of urinary oxalate release is 40 mg (440 μmol) in 24 hours. Men have a hardly higher conventional worth (43 mg/d in men versus 32 mg/d in women), yet this is basically a result of greater body habitus and greater ordinary supper size rather than to any certified normal metabolic difference. Stone advancement peril apparently depends more upon by and large full-scale oxalate release and obsession than on self-self-

assured conventional characteristics. Reflecting these customary characteristics, the normal importance of hyperoxaluria is urinary oxalate release that outperforms 40 mg/day. An elective significance of hyperoxaluria that reconsiders for size contrasts is 30 mg of urinary oxalate every 24 hours for each gram of released creatinine. Clearly, this astonishingly works with the docking issue. Eventually, it should be borne at the highest point of the need list that there are extra probably confining objections on the protein surface. While it is relied upon to be that the fundamental (known) site would be the one to partake in the bound transformation, there is no confirmation that this will be what is going on (Inbal *et al.,* 2002).

In vitro Calcium Oxalate Monohydrate Assays

The rate constraint of calcium oxalate important stone nucleation affected by ethanol and watery concentrate were settled and introduced in Fig. 1 and plate 1. To pick the Percentage check of calcium oxalate nucleation 15 fixation (0.1 mg to 1 mg/mL) of seeds watery and ethanolic dispense with were taken and added to the calcium chloride plan. By then the sodium oxalate game-plan was added and kept at 37˚C for 60 minutes. Later that aliquot of each focus was taken and seen under light intensifying point of convergence. In control all the pearl had hexagonal shape. The gem i.e., hexagonal outlined significant stone present in the control ought to be changed over either octahedral molded or round framed. Right when seen under enhancing point of convergence all concentrate treated models gem structure was viewed as octahedral. Out of 15 focuses utilized for this glance at. The difference in hexagonal to octahedral was doled out the retribution at 0.1 mg/mL. Also, the size of the jewels and number of the significant stones were viewed as reduced. Most unmistakable rate limit (91.44%) was seen in ethanolic eliminate accumulate with watery concentrate (73.59) at 9 mg/mL.

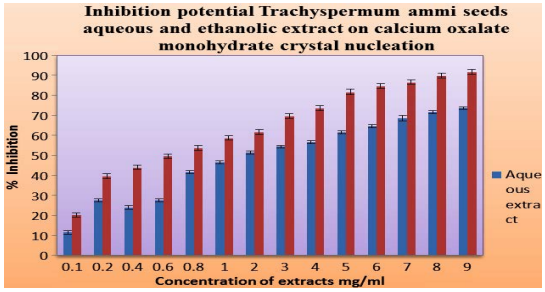


Fig. 1. Effect of *Trachyspermum ammi* Seeds Aqueous and Ethanolic Extract on Calcium oxalate monohydrate crystal nucleation

Calcium oxalate monohydrate (hexagonal shape) has more prominent affection towards regular layers of living creatures than calcium oxalate dihydrate (octahedral shape). In the current assessment, the seed concentrate of Trachyspermum ammi was found to can change over calcium oxalate monohydrate to calcium oxalate dihydrate jewels. Moreover, the concentrate can diminish the size of the formed octahedral valuable stones. Thus, in view of lessening in size and truly solubilizing limit made by seed concentrate will help with taking out the jewels from human body through pee.

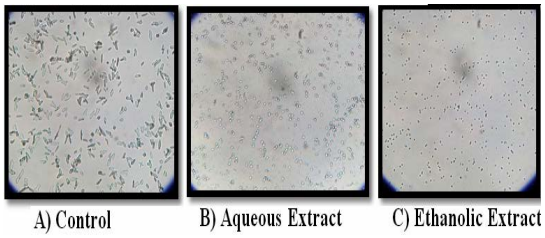


Plate 1. (A, B and C): Effect of *Trachyspermum ammi* Seeds Aqueous and Ethanolic Extract on Calcium oxalate monohydrate crystal nucleation

Our result was found inverse with Aggarwal *et al.,* (2010), When he gained 100% limitation of calcium oxalate monohydrate got while using 1000 µg/mL of watery concentrate of Tribulus terrestris. Pachana 2010 proposed that difference in calcium oxalate monohydrate to dihydrate may be a direct result of the presence of cyanidin, ascorbic destructive, citrus separate, succinic destructive and oxalic destructive that incited the prevention of calcium oxalate monohydrate nucleation.

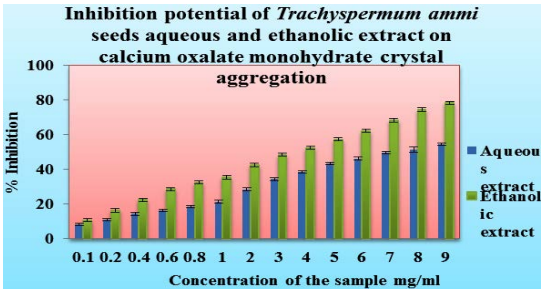


Fig. 2. Effect of *Trachyspermum ammi* Seeds Aqueous and Ethanolic Extract on Calcium oxalate monohydrate crystal Aggregation

The accompanying stage to diamond nucleation is aggregation that sets up the best instrument to grow the size of particle combination and plan of urinary stones (Das and Verma, 2008). Plate 3 and Fig. 3 depicts the results of rate block of diamond combination activated by the liquid and

ethanolic concentrate of Trachyspermum ammi. The added up to lots of valuable stones were found in the benchmark bunch. The aggregation was found to be diminished in the concentrates treated assembling on account of the inhibitory thought of the parts present in the plant against the complete of the calcium oxalate monohydrate valuable stones. Most prominent rate restriction (78.44) was seen in ethanolic eliminate amass with liquid concentrate (54.59) at 9 mg/mL. The agglomeration of the particles is an essential development in urinary stone plan, as greater diamonds are more unwilling to pass promptly in the urinary plot (kok, 1994).

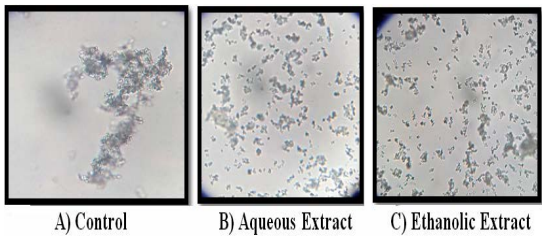


Plate 2. (A, B and C): Effect of *Trachyspermum ammi* Seeds Aqueous and Ethanolic Extract on Calciumoxalate monohydrate crystal aggregation

Bashir and Gilani, (2009) has revealed that the concentrate of Bergenia ligulata rhizome go likely as a good inhibitor of the calcium oxalate combination. Pareta *et al.,* (2010) had revealed that the Achyrantes indica inhibitorily influence important stone nucleation and total, which are huge for the treatment of urolithiasis. The third immense advancement in number related approach is gem improvement, which is a fundamental improvement in the urinary stone progression taking into account agglomeration of the particles. Fig. 2 and plate 4 portrays the headway of the calcium oxalate important stones inside seeing the fluid and ethanolic eliminates. To pick the Percentage snag of calcium oxalate headway 15 fixations (0.1 mg to 1 mg/mL) of seeds fluid and ethanolic concentrate of *Trachyspermum ammi* was taken and added to the calcium oxalate plan and kept at 37˚C for 60 minutes. Later that aliquot of each focus was taken and seen under light enhancing point of convergence. Minute perspective on calcium oxalate pearls showed that the gem size was more noticeable and especially amassed in charge. Regardless, the size of the important stone was extensively decreased and especially scattered by the hindrance of the ethanolic and watery concentrate of seeds of *Trachyspermum ammi*. Exactly when separated and fluid concentrate, ethanolic kill showed most incredible restriction. Most ludicrous rate block (68.44) was seen in ethanolic wipe out work with fluid concentrate (54.59) at 9 mg/mL. The outcomes were a huge load of clear that the seed disposes of diminished the gem headway undeniably which could at last obstruct the stone strategy.

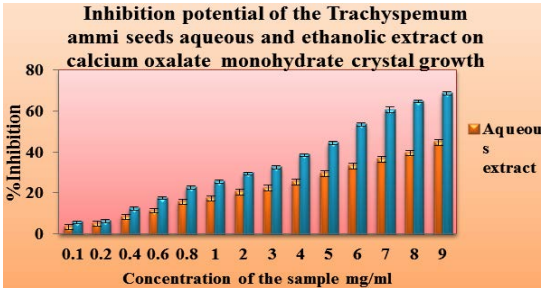


Fig. 3. Effect of *Trachyspermum ammi* Seeds Aqueous and Ethanolic Extract on Calcium oxalate monohydrate crystal growth

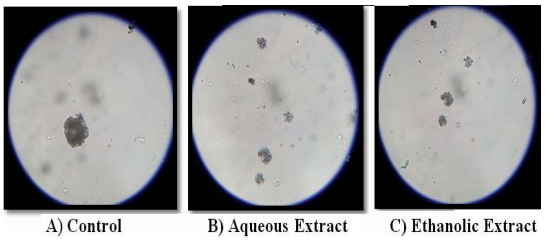


Plate 3. (A, B And C): Effect of *Trachyspermum ammi* Seeds Aqueous and Ethanolic Extract on Calcium oxalate monohydrate crystal growth

Beghalia *et al.,* (2008) have suggested in examinations using specific Algerian supportive plants *Chamaerops* humilis and *Tetraclinis ariculata* that might contain substance that limit the improvement of COM valuable stones. Our assessments are in amicability with the examinations that are as of late uncovered in the antiurolithiatic solid of *Tribulus terretris* on the improvement of calcium oxalate monohydrate pearls using twofold dispersal gel advancement methodology (Joshi *et al.,* 2005). The Table 1 depicts the recuperated data of bioactive blends from HPLC and GCMS examination of seeds of *Trachyspermum ammi* (Abdolali *et al.,* 2007: Mostafa *et al.,* 2004). These blends have been taken for the current sub-nuclear docking considers.

Table 1: List of Bioactive Compounds of Seeds of *Trachyspermum ammi*

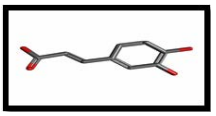
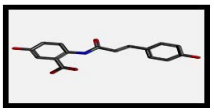
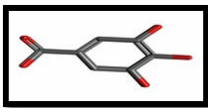
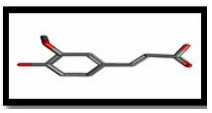
S. No	Bioactive Compounds
1	α-Pinene
2	Sabinene
3	α-Thujen
4	β-Pinene
5	Myrcene
6	α-Terpinene
7	ρ-Cymene
8	1,8-Cineole
9	Ocimene
10	γ-Terpinene
11	cis-Sabinene hydrate
12	Linalool
13	trans-Sabinene hydrate
14	Cyclocitral
15	Terpinen-4-ol
16	α-Terpineol
17	Thymol
18	Carvacrol
19	Styrene
20	Camphene
21	δ-3-Carene
22	β-Phellandrene
23	Terpinolene
24	Terpine-1-ol
25	Trans-β-Ocimene

Table 2: Disease Receptors and Its Protein ID

S.No	Disease	Receptors	Protein ID
1	Urolithiasis(hyperoxaluria)	Glycolytic oxidase	IUBP
2	Urolithiasis (infection stones)	Urease	2YVS

The Lipinski's standard is critical for drug progression where a pharmacologically unique lead structure is overhauled step-wise for extended activity and selectivity, similarly as prescription like properties. Lipinski's standard says, it has near 5 hydrogen bond givers, not more than 10 hydrogen bond acceptors, nuclear burden under 500 Dalton, Partition coefficient A Log P under 5. The development of the phytocompounds from the seed basic oil of *Trachyspermum ammi* explicitly a) Carvacrol, b) Linalool, c) Thymol and d) Cyclocitral, three dimensional plans were made by chemsketch 12.0 programming and besides evaluated the Lipinski's properties this was showed up in Table 4. In the current examination, recently referenced phytocompounds were gotten from the seed basic oil of *Trachyspermum ammi* satisfies the five standards of Lipinski's properties. Medicine similarity considers are an obvious undertaking to appreciate the substance properties that make particles either productive or maybe expensive clinical disillusionments. The receptors perceived for the singular ailments in the present in silico examination have been given in the Table 3.

Table 3: Lipinski's Properties of The Four Compounds of Seeds of *Trachyspermum ammi*

Ligand molecule	Molecular weight [g/mol]	Molecular Formula	Xlogp 3 value (<=5)	H- bond donor	H-bond acceptor	Structure
Linalool	299.27812	$C_7H_6O_2$	1.3	2	2	
Thymol	180.15742	$C_9H_8O_4$	1.4	4	3	
Carvacrol	194.184	$C_{10}H_{10}O_4$	1.6	3	3	
Cyclocitrol	170.11954	$C_7H_6O_5$	0.9	1	4	

To guarantee that the ligand direction and sensible restricting methods of the inhibitors, the Ligand Fit program docking boundaries must be first approved for the gem design's active site. Protein Utilities and Health convention of discovery's studio was utilized to discover the dynamic destinations in the design and it was observed that the dynamic site contains amino acids like ASP, ARG, GUU and GLU. Aftereffects of docking showed that not really set in stone the ideal direction of the docked inhibitor, precisely to these dynamic locales. Here highest-level ligands were taken for restricting liking studies.

The approval cycle comprised of two sections:

1. Hydrogen bond subtleties of the highest level docked present.
2. Prediction of Binding energy between the docked ligand and the chemical utilizing different score determined utilizing discovery studio.

A high charismas score is appropriate for better protein-ligand connection (Muegge *et al.,* 2006) According to (Trapani *et al.,* 1992) hydrogen holding is probably a fundamental necessity for some medication receptor connections. A solitary hydrogen bond is somewhat powerless and would not be relied upon to help a medication receptor association alone, however when numerous hydrogen bonds are framed among medications and receptors, as is ordinarily the situation, a lot of strength is given upon the medication receptor cooperation.

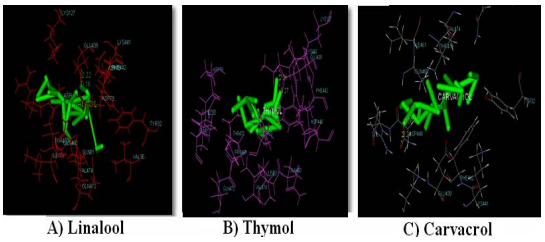


Plate 4. (A, B And C) Docking Analysis Between the Receptor Glycolate Oxidase (IUBP) With Ligand Molecules Derived from Seed Compounds of *Trachyspermum ammi*

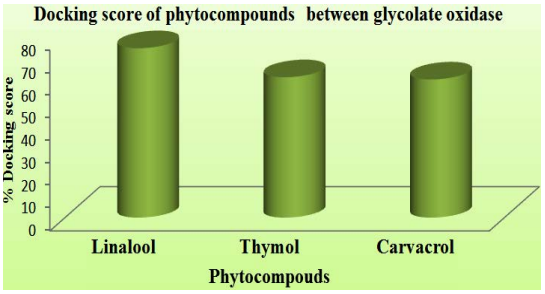


Fig. 4. Dock Score of Ligand Molecules Interact with IUBP

Table 4: Hydrogen Bonding Interactions Between the Receptor Glycolate Oxidase with Ligand Molecules

Ligand Molecules	Amino acid	Atoms in amino acid	Position	Atoms in ligand	H-Bond length	H-bond	Dock score
Linalool	GUU	H21	439	OE1	0.62		
Linalool	GUU	H21	439	OE2	2.38	2	75.101
Thymol	GLU	439	439	OE1	0.45		
Thymol	GLU	439	439	OE2	1.75	2	62.244
Carvacrol	ASP	H25	448	OO1	1.94		
Carvacrol	ASP	H25	448	OO2	2.24	2	61.244

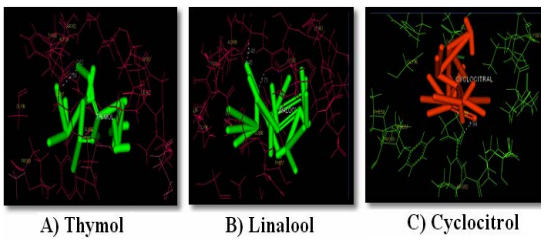


Plate 5. (A, B And C) Docking Analysis Between the Receptor Urease (2YVS) With Ligand Molecules Derived from Seed Compounds of *Trachyspermum ammi*

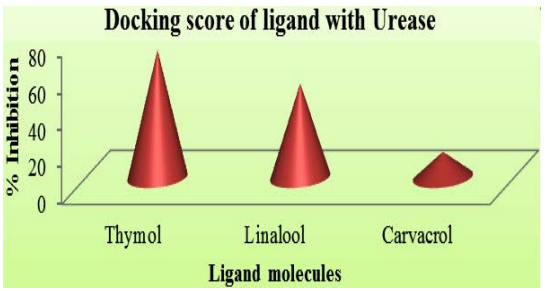


Fig. 5. Dock Score of Ligand Molecules Interact with 2YVS

Table 5: Hydrogen bonding interactions between the receptor Urease with ligand molecules

Ligand Molecules	Amino acid	Atoms in amino acid	Position	Atoms in ligand	H-Bond length	H-bond	Dock score
Thymol	ASP	H25	89	OO1	0.62		
	ASP	H25	89	OO2	2.38	2	69.468
	ARG	HH21	92	O1	0.45		
Linalool	ASP	H21	89	OO1	1.75	3	51.217
	ASP	H21	89	OO2	0.45		
Cyclocitral	ARG	HH22	92	O1	1.94	1	13.924

Subsequently, the seeds of *Trachyspermum ammi* showed a basic level of antilithiatic development both under in vitro and in silico conditions. The secret arrangement of the effect of the seed focuses of

Trachyspermum ammi on lithiasis is now muddled, yet the effect is clearly related to extended diuresis and cuts down the urinary centralization of stone molding constituents. The alkaloids, flavonoids, saponins, tannins and triterpenoids present in the seeds concentrate may be the responsible for antilithiatic development. These disclosures thusly concise the requirement for extra examination to do the separation of dynamic constituents from the seeds of *Trachyspermum ammi* to fix the stone course of action.

RESULT AND DISCUSSION

In this current assessment, out of 4 compound,3 compounds docked with IUBP, usually the amino acids attracted with the receptor and ligand coordinated effort were GUU, GLU and ASP in Table 5. The relationship among Linalool and glycolate oxidase shows most brought harbor score 75.101 up in Fig. 5. wandered from different mixes. Close to this compound Thymol showed most critical dock score 62.244 with the receptor. Among the three ligands carvacrol showed low dock score 61.244 considering weak relationship with the receptor. In this current assessment, out of 4 compound 3 mixes docked with 2YVS, all things considered the amino acids related with the receptor and ligand affiliation were ARG and ASP in Table 6. The coordinated effort among Thymol and glycolate oxidase showed most brought dock score 69.468 up in Fig. 5. wandered from different mixes. Close to this compound Linalool showed most fundamental dock score 51.217 with the receptor. Among the three ligands cyclotol showed low dock score 13.924 by virtue of sensitive relationship with the receptor.

CONCLUSION

In vitro assessment against urolithiasis displays that the seeds fluid and ethanolic separate have inhibitory action against calcium oxalate monohydrate precious stone nucleation, accumulation and progression. Of the two-dispense with attempted ethanolic separate have more expected limitation than fluid concentrate. For in silico appraisal, 25 bioactive mixes from seeds of *Trachyspermum ammi* were taken ward on HPLC and GCMS assessment and 2 receptors inducers of urolithiasis were picked subject to open piece. These picked bioactive mixes were filled in as ligands. The two ligands and receptors introduced to in silico assessment utilizing accelory openness studio 2.1. The mixes Thymol, Linalool and Carvacrol showed most raised moor score, low bond and unimaginable hydrogen bond relationship with Glycolate oxidase receptor. The mixes Thymol, Linalool and Cyclocitral showed most basic dock score, low bond and unbelievable hydrogen bond collaboration with Urease receptor. Out of these four mixes Thymol and Linalool showed most basic relationship with the two receptors.

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