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Exploring the Molecular Docking Interactions between the Polyherbal Formulation Ibadhychooranam and Human Aldose Reductase Enzyme as a Novel Approach for Investigating its Potential Efficacy in Management of Cataract

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Abstract:-

➢ ***Background:***

Kannir sirandha urupillai… which means no organ is better than eye. Eye health and treatment have held significant importance in the Siddha system of medicine since ancient times, emphasizing the holistic approach to well-being encompassing physical, mental, and spiritual aspects. Eye disease is classified into 96 types and their ethology, treatment method, preventive measures all are explained in many of the Siddha literature. Among them cataract is one of the leading cause of blindness which is characterised by clouding of eye's natural lens, leading to blurry, foggy or flimy vision. This paper will elaborates about the docking analysis of poly herbal formulation Ibadhy chooranam against Human aldose reductase enzyme for cataract.

➢ ***Aim & Objective:***

The aim of this study is to investigate the potential efficacy of the polyherbal formulation IbadhyChooranam in preventing or treating cataracts through molecular docking analysis of its interactions with the human aldose reductase enzyme.

➢ ***Methodology:***

Docking simulations were conducted for the extracted phytoconstituents of IbadhyChooranam against the Human Aldose Reductase Enzyme. AutoDock tools were utilized to incorporate hydrogen atoms, Coleman united atom type charges, and solvation parameters. The docking process employed the Lamarckian genetic algorithm along with the Solis & Wets Local Search method to simulate ligand-receptor interactions.

➢ ***Result:***

The current study revealed that phytochemicals present in IbadhyChooranam, including Nerolidol, Ellagic acid, Phyllanthin, Costunolide, Embelin, Cyperolone, Zingiberene, Piperic acid, Piperine, and Lupeol, exhibited between 6 to 9 significant interactions with residual amino acids in the aldose reductase enzyme. In comparison, the standard drug Epalrestat demonstrated 8 viable interactions with the residual amino acids of the aldose reductase enzyme.

➢ ***Conclusion:***

According to the computational analysis findings, it can be inferred that the bioactive compounds present in IbadhyChooranam exhibit notable binding affinity towards the target aldose reductase enzyme. Ibadhy chooranam inhibit the function of aldose reductase enzyme which delay the sorbitol accumulation and subsequent cataract development. Through this study, it was also justified that the Ibadhy chooranam possess significant anti-cataract activity.

Keywords:- *Ibadhy Chooranam, Cataract, Kann Kasam, Siddha Medicine, Kann Noigal.*

I. INTRODUCTION

The primary goal of Siddha medicine is to achieve physical, mental and spiritual well-being by restoring harmony and equilibrium within the body. It utilizes a wide range of natural remedies, including herbal medicines, minerals, metals, animal products, diet and lifestyle modifications alongwith therapeutic practices such as yoga, meditation and detoxification techniques. Among the five sense organs, Eye is the very sensitive organ which is denoted as "Kannir sirandha urupillai…" which means no organ is better than eye. In the Siddha system of medicine, the emphasis on eye care and treatment dates back to ancient times, reflecting its enduring significance throughout history. Eye disease is classified into 96 types and their ethology, treatment method, preventive measures all are explained in many of the Siddha literature. Among them cataract is one of the leading cause of blindness which is characterised by clouding of eye's natural lens, leading to blurry, foggy or flimy vision. This paper will elaborates about the docking analysis of poly herbal formulation

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Ibadhy chooranam against Human aldose reductase enzyme for cataract.

II. MATERIALS AND METHODS

The trial drug IbadhyChooranam, sourced from the Siddha text "AgathiyarNagamuniNayanavidhi 200," is specifically recommended for the treatment of various eye ailments, often administered with sugar as an adjuvant.

"Elam lavangam nellimulli isaindha kottam vaivilangam moola muthanth thirikadugu moorik kadukkai samanagach
salach sivadhai saman kondu sariyai sarkarai dhan kooti kalai poludhe konda kaal kannil rogam kalindhidume."

➢ *Objectives:*

The efficacy of IbadhyChooranam in controlling cataracts was assessed through docking experiments. The phytocomponents were found to bind to key amino acids (Trp20, Val47, Tyr48, Trp79, His110, Trp111, Thr113, Phe122, Gln183, Tyr209, Ala299, and Leu300) of the aldose reductase enzyme, forming hydrogen bonds and inhibiting its activity. This enzyme plays a pivotal role in converting glucose to sorbitol, a critical step in cataract formation. Additionally, aldose reductase is implicated in lens epithelial cell apoptosis. Phytocomponents that selectively inhibit aldose reductase function can delay sorbitol accumulation and consequent cataract development.

- PDB : Name Of the Target
- 4GCA : Human Aldose reductase enzyme

III. METHODOLOGY

Methodology for Molecular Docking Analysis of IbadhyChooranam for Cataract Management:Selection of Ligands and Receptor: Identify the bioactive compounds present in IbadhyChooranam using available databases or computational prediction methods. Retrieve the crystal structure of the human aldose reductase enzyme from relevant databases.Preparation of Ligands and Receptor: Use molecular modeling software to prepare the 3D structures of the ligands and receptor. This involves adding hydrogen atoms, assigning bond orders, and optimizing the geometry of the ligands and receptor.Grid Generation: Define the binding site of the receptor by generating a grid around it. This step helps in restricting the search space for ligand binding and improves docking efficiency.Parameterization and Scoring Functions: Assign appropriate force field parameters and scoring functions to the ligands and receptor to accurately predict binding affinities and interactions.Docking Simulations: Perform molecular docking simulations using a suitable docking algorithm, such as Lamarckian genetic algorithm or AutodockVina. Dock the ligands into the binding site of the receptor and allow for conformational flexibility if necessary.Analysis of Docking Results: Analyze the docking results to identify potential binding poses and interactions between the ligands and receptor. Evaluate the binding affinities and select the most favorable binding modes based on docking scores and visual inspection.Validation: Validate the docking results by comparing them with experimental data, if available, or by conducting additional in vitro or in vivo studies to confirm the predicted interactions and efficacy of the ligands in cataract management.Interpretation and Conclusion: Interpret the docking results in the context of cataract pathophysiology and the mechanism of action of the aldose reductase enzyme. Draw conclusions regarding the potential efficacy of IbadhyChooranam in cataract management based on the docking analysis.Future Directions: Propose future research directions, including experimental validation and clinical studies, to further explore the therapeutic potential of IbadhyChooranam in cataract management and advance its development as a potential treatment option.

Table 1: List of Phytocomponents Selected for Docking

Elettariacardamom	**Nerolidol [5]**
Syzygium aromaticum	Ellagic acid [6]
Phyllanthus emblica	Phyllanthin [7]
Saussurea lappa	Costunolide [8]
Embelia ribes	Embelin [9]
Cyperus rotundus	Cyperolone [10]
Zingiber officinale	Zingiberene [11]
Piper nigrum	Piperic acid [12]
Piper longum	Piperine [13]
Terminalia chebula	Gallic acid [14]
Operculina turpethum	Lupeol [15]

➢ *Standard Drug – Epalrestat*

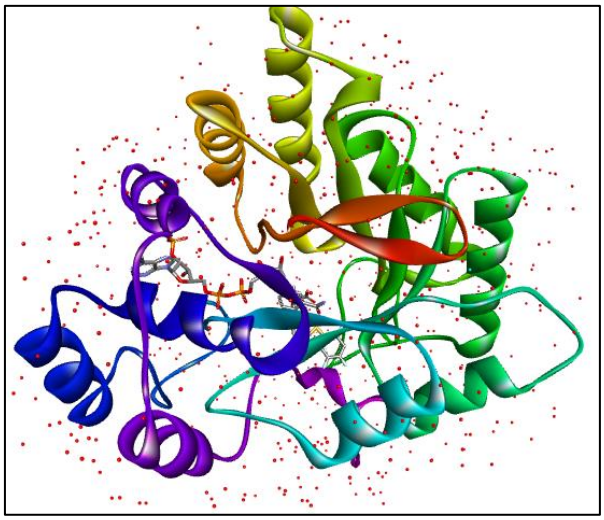

Fig 1: 3D- Structure of Human Aldose reductase enzyme (PDB) - 4GCA

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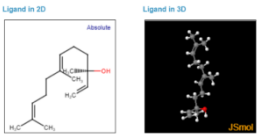
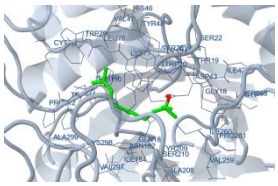
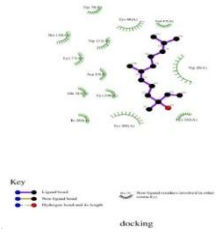
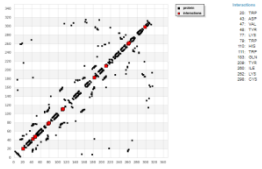
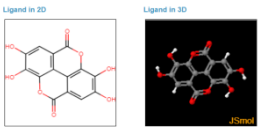
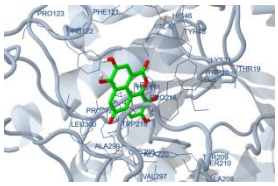
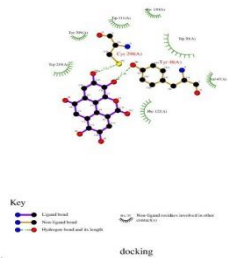
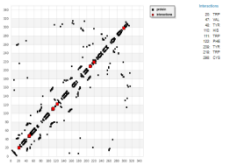
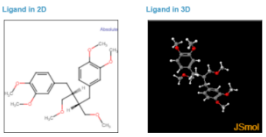
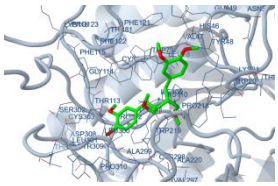
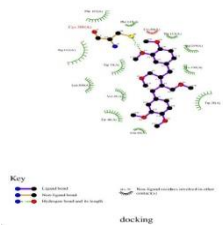
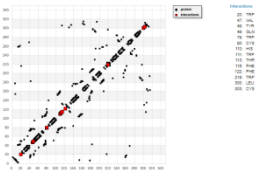
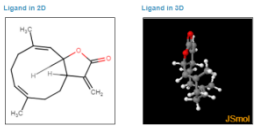
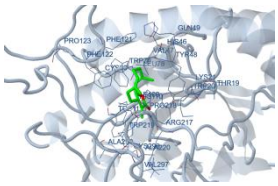
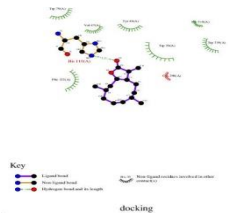
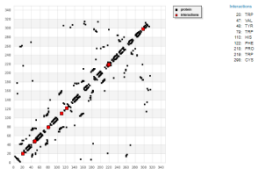
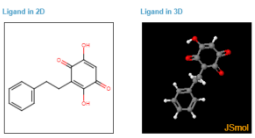
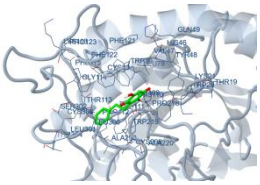
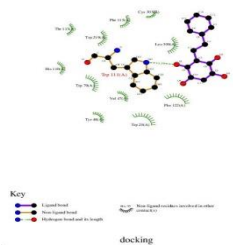
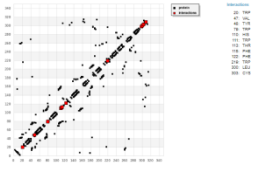
Table 2: Phyto Components - 2d and 3d Structure, Docking Pose with Human Aldose Reductase Enzyme (Pdb) - 4gca, 2d Interaction Plot And Hydrogen Bond Plotting with Core Amino Acids

2D and 3D Structure of phytocomponents	Docking Pose of phytocomponents with Human Aldose reductase enzyme (PDB) - 4GCA	2D Interaction Plot Analysis	Hydrogen bond plotting with core amino acid Analysis
Nerolidol 			
Ellagic acid 			
Phyllanthin 			
Costunolide 			
Embelin 			

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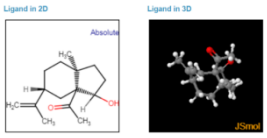
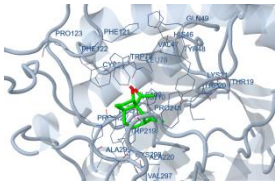
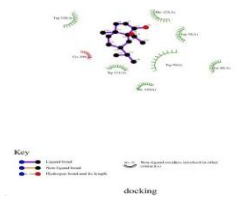
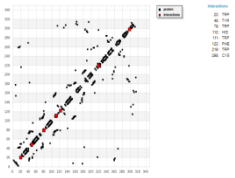
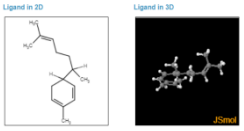
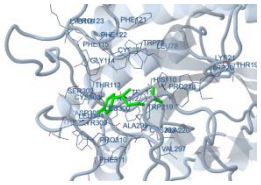
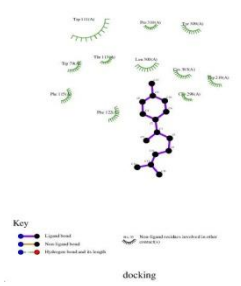
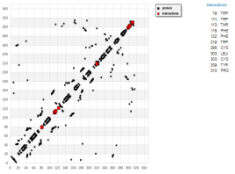
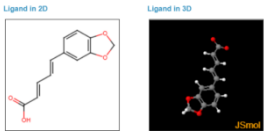
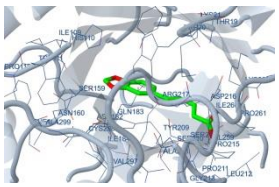
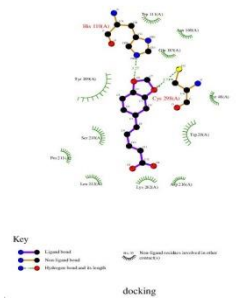
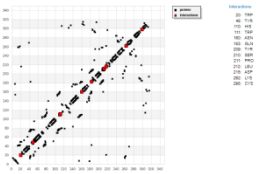
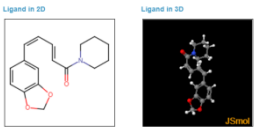
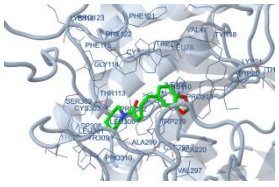
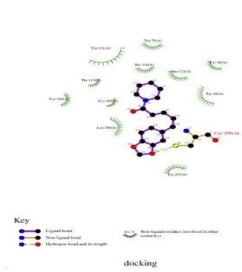
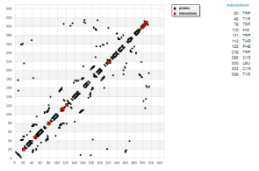
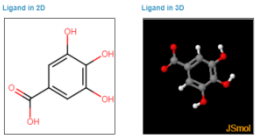
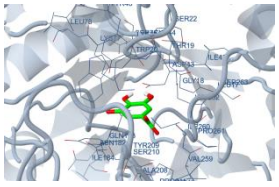
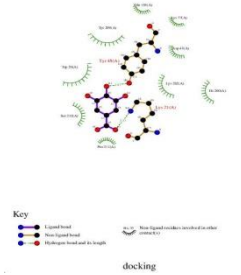
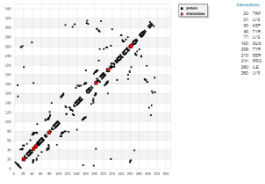
Cyperolone 			
Zingiberene 			
Piperic acid 			
Piperine 			
Gallic acid 			

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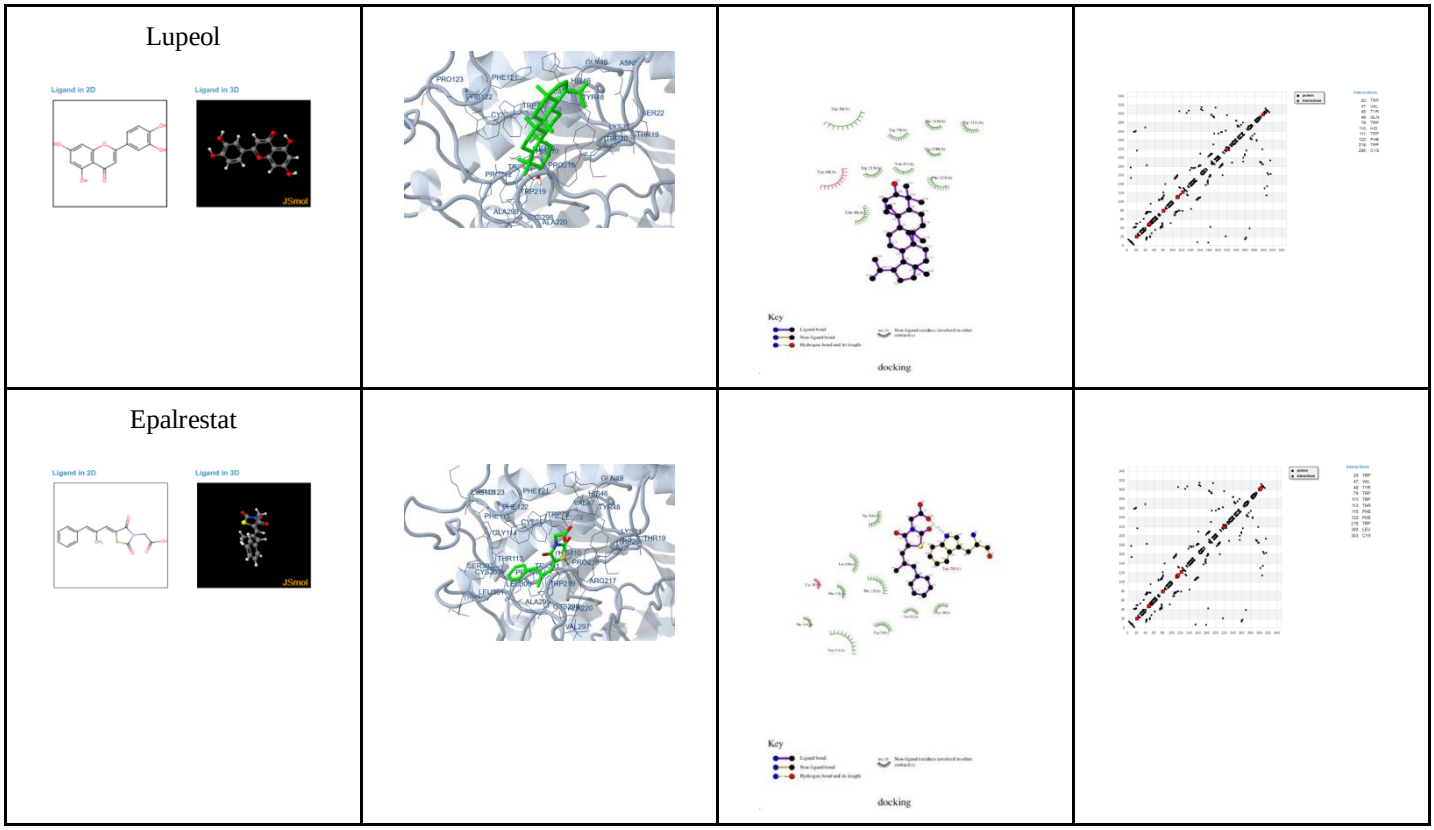

Table 3: Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Nerolidol	222.37 g/mol	$C_{15}H_{26}O$	1	1	7
Ellagic acid	302.194 g/mol	$C_{14}H_6O_8$	4	8	0
Phyllanthin	418.5 g/mol	$C_{24}H_{34}O_6$	0	6	13
Costunolide	232.323 g/mol	$C_{15}H_{20}O_2$	0	2	0
Embelin	294.4 g/mol	$C_{17}H_{26}O_4$	2	4	10
Cyperolone	236.35 g/mol	$C_{15}H_{24}O_2$	1	2	2
Zingiberene	204.35 g/mol	$C_{15}H_{24}$	0	0	4
Piperic acid	218.2 g/mol	$C_{12}H_{10}O_4$	1	4	3
Piperine	285.34 g/mol	$C_{17}H_{19}NO_3$	0	3	3
Gallic acid	170.12 g/mol	$C_7H_6O_5$	4	5	1
Lupeol	426.7g/mol	$C_{30}H_{50}O$	1	1	1
Epalrestat	319.4 g/mol	$C_{15}H_{13}NO_3S_2$	1	5	4

Table 4: Summary of the Molecular Docking Studies of Compounds Against Human Aldose Reductase Enzyme (Pdb) - 4gca

Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Nerolidol	-7.79 kcal/mol	1.94 uM	-0.14 kcal/mol	-9.97 kcal/mol	693.759
Ellagic acid	-7.86 kcal/mol	1.73 uM	-0.06 kcal/mol	-6.71 kcal/mol	652.95
Phyllanthin	-8.54 kcal/mol	554.13 nM	-0.03 kcal/mol	-12.60 kcal/mol	972.099
Costunolide	-7.53 kcal/mol	3.02 uM	-0.03 kcal/mol	-7.53 kcal/mol	650.158
Embelin	-7.81 kcal/mol	1.90 uM	-0.06 kcal/mol	-8.22 kcal/mol	628.466
Cyperolone	-7.15 kcal/mol	5.71 uM	+0.00 kcal/mol	-7.31 kcal/mol	638.507
Zingiberene	-8.61 kcal/mol	486.01 nM	-0.00 kcal/mol	-9.59 kcal/mol	639.279
Piperic acid	-7.43 kcal/mol	3.56 uM	-0.55 kcal/mol	-8.29 kcal/mol	584.279
Piperine	-9.97 kcal/mol	49.43 nM	-0.01 kcal/mol	-10.48 kcal/mol	715.956
Gallic acid	-5.79 kcal/mol	56.98 uM	-1.04 kcal/mol	-5.28 kcal/mol	431.218
Lupeol	-10.06 kcal/mol	42.23 nM	-0.01 kcal/mol	-10.77 kcal/mol	874.311
Epalrestat	-9.90 kcal/mol	55.17 nM	-0.85 kcal/mol	-11.24 kcal/mol	725.143

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Table 5: Amino Acid Residue Interaction of Lead Against Human Aldose Reductase Enzyme (PDB) - 4gca

Compound	Interactions	Amino acid Residues													
Nerolidol	8	20	43	47	48	77	79	110	111	183	209	260	262	298	
		TRP	ASP	VAL	TYR	LYS	TRP	HIS	TRP	GLN	TYR	ILE	LYS	CYS	
Ellagic acid	7	20	47	48	110	111	122	209	219	298					
		TRP	VAL	TYR	HIS	TRP	PHE	TYR	TRP	CYS					
Phyllanthin	9	20	47	48	49	79	80	110	111	113	115	122	219	300	303
		TRP	VAL	TYR	GLN	TRP	CYS	HIS	TRP	THR	PHE	PHE	TRP	LEU	CYS
Costunolide	6	20	47	48	79	110	122	218	219	298					
		TRP	VAL	TYR	TRP	HIS	PHE	PRO	TRP	CYS					
Embelin	9	20	47	48	79	110	111	113	115	122	219	300	303		
		TRP	VAL	TYR	TRP	HIS	TRP	THR	PHE	PHE	TRP	LEU	CYS		
Cyperolone	6	20	48	79	110	111	122	219	298						
		TRP	TYR	TRP	HIS	TRP	PHE	TRP	CYS						
Zingiberene	6	79	111	113	115	122	219	298	300	303	309	310			
		TRP	TRP	THR	PHE	PHE	TRP	CYS	LEU	CYS	TYR	PRO			
Piperic acid	6	20	48	110	111	160	183	209	210	211	212	216	262	298	
		TRP	TYR	HIS	TRP	ASN	GLN	TYR	SER	PRO	LEU	ASP	LYS	CYS	
Piperine	8	20	48	79	110	111	113	122	219	298	300	303	309		
		TRP	TYR	TRP	HIS	TRP	THR	PHE	TRP	CYS	LEU	CYS	TYR		
Gallic acid	4	20	21	43	48	77	183	209	210	211	260	262			
		TRP	LYS	ASP	TYR	LYS	GLN	TYR	SER	PRO	ILE	LYS			
Lupeol	7	20	47	48	49	79	110	111	122	219	298				
		TRP	VAL	TYR	GLN	TRP	HIS	TRP	PHE	TRP	CYS				
Epalrestat	8	20 TRP	47 VAL	48 TYR	79 TRP	111 TRP	113 THR	115 PHE	122 PHE	219 TRP	300 LEU	303 CYS			

IV. OBSERVATION AND INFERENCE

The study identified a total of 11 bioactive lead compounds extracted from the herbs within the Siddha formulation. Analysis revealed that compounds such as Nerolidol, Ellagic acid, Phyllanthin, Costunolide, Embelin, Cyperolone, Zingiberene, Piperic acid, Piperine, and Lupeol displayed between 6 to 9 significant interactions with residual amino acids within the target aldose reductase enzyme. Interestingly, these interactions surpassed those observed with the standard drug Epalrestat, which demonstrated 8 viable interactions with the enzyme's residual amino acids.

V. DISCUSSION

Siddha system classifies Eye disease into 96 types which describes disease of the black part of eye into 45 types. One among them is Cataract (Kasam) which is characterized by severe pain in centre of eye's, headache, blurry vision, excessive lacrymation which is due to age related factors, congenital factors, environmental changes or trauma. Ibadhy chooranam metioned in Siddha literature has antioxidant, neuroprotective and anti-inflammatory activity. As per the Gunapadam Mooligai literature evidence and pharmacological activities of the ingredients present in the Ibadhy chooranam shows that - Kirambu cures kann poo, Nellimulli has the property of Opthalmic disorder modulator, Kostam cures Kann noigal, Thippili and Kadukkai also cures Kann noigal. Cataract is one of the leading cause of blindness. Surgery is the only solution given today to recover Cataract. But it leads to various complications such as visual axis opacification, glaucoma, uveal inflammation, retinal detachment, corneal astigmatism etc. To reduce the post surgery complications and to prevent Cataract in earlier stage Siddha polyherbal formulation Ibadhy chooranam will be very effective.

VI. CONCLUSION

Based on the computational analysis results, it was determined that bioactive compounds including Nerolidol, Ellagic acid, Phyllanthin, Costunolide, Embelin, Cyperolone, Zingiberene, Piperic acid, Piperine, and Lupeol found in the herbs exhibit notable binding affinity towards the target aldose reductase enzyme. These compounds interact with active amino acids within the enzyme's active site, suggesting their potential to inhibit aldose reductase function and consequently delay sorbitol accumulation, thereby mitigating cataract development. Furthermore, the observed interactions support the significant anti-cataract activity of these phytochemicals.

➢ *Disclaimer:*

The findings presented in this molecular docking study are based solely on computational analysis and in silico predictions. While efforts have been made to ensure accuracy and reliability, it is important to note that computational simulations may not fully replicate biological complexities observed in vivo. Therefore, the results should be interpreted with caution and further validated through experimental studies, including in vitro assays and preclinical investigations. Additionally, this study does not constitute medical advice or treatment recommendations. Individuals should consult healthcare professionals before making any decisions related to their health or medical treatment.

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➢ *Consent*

By participating in this molecular docking study, you acknowledge that your data, including any personal information provided, may be used for research purposes. You understand that the study involves computational analysis of molecular interactions and does not involve any clinical interventions or medical procedures. Your participation is voluntary, and you have the right to withdraw at any time without penalty. You understand that the results of the study may be published or disseminated in scientific publications or presentations but your identity will remain confidential. If you have any questions or concerns about the study, you may contact the principal investigator for clarification.

➢ *Ethical Approval:*

Not applicable.

➢ *Competing Interests:*

The authors declare that they have no competing interests related to the molecular docking study described in this research. The study was conducted with integrity and transparency, and the findings are presented objectively without any bias or influence from external parties.

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