

In Silico Molecular Docking Studies of Plumbago Zeylanica L. Against Androgen receptor in Prostate cancer

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Additional Declarations: No competing interests reported.

Abstract

Introduction:

In Siddha medicine, a number of herbs are mentioned as possible cancer therapies, both alone and in combination. Such one of the best herb mention in siddha literature is Ven Kodiveli/ Ven chithramoolam. (Plumbago zeylanica L.) which is an extremely powerful herb with wide distribution, and also component of many Siddha drugs Like Chitramoola kuligai, chithramoola thylam etc. In that chithra moola kuligai is specially indicated for Yoni putru (Vaginal cancer), linga putru (Penile cancer, Prostate cancer), Vippuruthi (All types of cancers). The objective of this study is performing in silico computational analyses of phytoconstituents in extracts of the root of Plumbago zeylanica against antrogen receptor for prostate cancer

Methodology:

Docking calculations were carried out for retrieved phytocomponents of Plumbago zeylanica against the target Androgen receptor. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools .

Observation and inference:

Total of 5 bioactive lead compounds were retrieved from the herbal ingredients. From reported data of the herb, the phytochemicals such as Lupeol and Stigmasterol reveals maximum of 5 interactions followed by which the compounds such as Plumbagin, Oleic Acid and β -Asarone reveals maximum of 4 interactions with the core active amino acid residues present on the target androgen receptor.

Conclusion:

Based on the results of the computational analysis it was concluded that the bio-active compound's like Lupeol and Stigmasterol, Plumbagin, Oleic Acid and β -Asarone present in the herbal ingredients possess significant binding affinity towards androgen receptor thereby it may greatly inhibits progression of prostate cancer. Further clinical trials would be beneficial in determining whether this herb is an effective therapy for prostate cancer.

INTRODUCTION

Cancer is a serious global health concern. It is estimated that 1.46 million cases of cancer occurred in India in 2022, and by 2025, that number is expected to climb to 1.57 million. ⁽¹⁾ According to studies, prostate cancer is the fifth most prevalent disease overall and the second most common cancer in men diagnosed globally. ⁽²⁾ Elderly people are predominantly affected by prostate cancer. It ranks as the sixth most common cause of cancer-related deaths among men. Because of the advantages and significance of traditional medicine, the World Health Organisation has designated integrative oncology as one of the main goals of cancer therapy. In Siddha medicine, a number of herbs are mentioned as possible cancer therapies, both alone and in combination. Such one of the best herb mention in siddha literature is Ven Kodiveli/ Ven chithramoolam. (Plumbago zeylanica L.) which is an extremely powerful herb with wide distribution, and also component of many Siddha drugs Like Chitramoola kuligai, chithramoola thylam etc. In that chithra moola kuligai is specially indicated for Yoni putru (Vaginal cancer), linga putru (Penile cancer, Prostate cancer), Vippuruthi (All types of cancers). The objective of this study is performing in silico computational analyses of phytoconstituents in extracts of the root of Plumbago zeylanica against antrogen receptor for prostate cancer.

OBJECTIVE:

Binding of phyto components with the core amino acids (Leu 873, Gly 708, Arg 752, Met 745, Gln 711 and Met 749) of the target by forming hydrogen bond will hinder the function of the Human androgen receptor with PDB – 1E3G. The target androgen receptor highly involved in initiation and progression of prostate cancer by contributing to proliferation and differentiation of prostate epithelial cells during development of androgen dependent Prostate Cancer. Thereby phyto components which occupies the active amino acids on the androgen receptors will hinder its function and may act as a potential therapeutic agent for management of prostate cancer.

PDB	Name of the Target
1E3G	Androgen receptor

3D- Structure of Androgen receptor (PDB)-1E3G

RECEPTOR STRUCTURE

Crystalline structure of the target enzyme Androgen receptor (PDB) - 1E3G was retrieved from protein data bank and protein clean-up process was done and essential missing hydrogen atom were being added. Different orientation of the lead molecules with respect to the target protein was evaluated by Autodock program and the best dock pose was selected based on the interaction study analysis.

METHODOLOGY

Docking calculations were carried out for retrieved phytocomponents against the target Androgen receptor. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (Morris, Goodsell et al., 1998). Affinity (grid) maps of $\times \times$ Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris, Goodsell et al., 1998). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1987). Initial position, orientation, and torsions of the ligand

molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

2D and 3D Structure of Selected Ligands

Table 1: Ligand Properties of the Compounds Selected for Docking Analysis

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Plumbagin	188.182 g/mol	C ₁₁ H ₈ O ₃	1	3	0
Oleic Acid	282.5 g/mol	C ₁₈ H ₃₄ O ₂	1	2	15
β-Asarone	208.25 g/mol	C ₁₂ H ₁₆ O ₃	0	3	4
Lupeol	426.7 g/mol	C ₃₀ H ₅₀ O	1	1	1
Stigmasterol	412.7g/mol	C ₂₉ H ₄₈ O	1	1	5

Table 2: Summary of the molecular docking studies of compounds against Androgen receptor (PDB) - 1E3G

Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Plumbagin	-6.51 kcal/mol	17.04 uM	-0.13 kcal/mol	-6.80 kcal/mol	371.224
Oleic Acid	-4.50 kcal/mol	506.48 uM	-0.20 kcal/mol	-4.79 kcal/mol	300.18
β-Asarone	-5.22 kcal/mol	149.17 uM	-0.09 kcal/mol	-6.45 kcal/mol	465.787
Lupeol	-2.51 kcal/mol	14.52 mM	-0.06 kcal/mol	-4.78 kcal/mol	665.339
Stigmasterol	-3.25 kcal/mol	4.12 mM	+0.02 kcal/mol	-5.46 kcal/mol	654.167

Table 3: Amino acid Residue Interaction of Lead againstAndrogen receptor (PDB) - 1E3G

Compounds	Interactions	Amino acid Residues															
Plumbagin	4	704	707	711	745	746	749	752	764								
		LEU	LEU	GLN	MET	VAL	MET	ARG	PHE								
Oleic Acid	4	704	707	711	745	746	749	764	787	873							
		LEU	LEU	GLN	MET	VAL	MET	PHE	MET	LEU							
β-Asarone	4	704	705	707	711	745	746	749	764	787	873						
		LEU	ASN	LEU	GLN	MET	VAL	MET	PHE	MET	LEU						
Lupeol	5	704	705	707	711	742	745	749	752	764	780	873	876	877	880	891	895
		LEU	ASN	LEU	GLN	MET	MET	MET	ARG	PHE	MET	LEU	PHE	THR	LEU	PHE	MET
Stigmasterol	5	701	704	705	707	711	742	745	746	749	752	764	780	873	876	877	880
		LEU	LEU	ASN	LEU	GLN	MET	MET	VAL	MET	ARG	PHE	MET	LEU	PHE	THR	LEU

OBSERVATION AND INFERENCE

Total of 5 bioactive lead compounds were retrieved from the herbal ingredients. From reported data of the herb, the phytochemicals such as Lupeol and Stigmasterol reveals maximum of 5 interactions followed by which the compounds such as Plumbagin, Oleic Acid and β-Asarone reveals maximum of 4 interactions with the core active amino acid residues present on the target androgen receptor.

Conclusion

Based on the results of the computational analysis it was concluded that the bio-active compound's present in *Plumbago zeylanica L.* like Lupeol and Stigmasterol, Plumbagin, Oleic Acidand β-Asarone possess significant binding affinity towards androgen receptor thereby it may greatly inhibits progression of prostate cancer by limiting the proliferation and differentiation of prostate epithelial cells during development of prostate Cancer. Thereby phyto

components which occupies the active amino acids on the androgen receptors will hinder its function and may act as a potential therapeutic agent for management of prostate cancer.

Declarations

Funding Declaration

No funding.

Competing Interests

No competing interests.

Author Contribution

Dr.S.Siva Lakshmi wrote the main manuscript textDr.A.Aishwarya, T.Monika prepared figures and table DR.H.Vedha Merlin Kumari , Dr.T.Lakshmi Kantham and R.Meenakumari reviewed the manuscript

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Figures

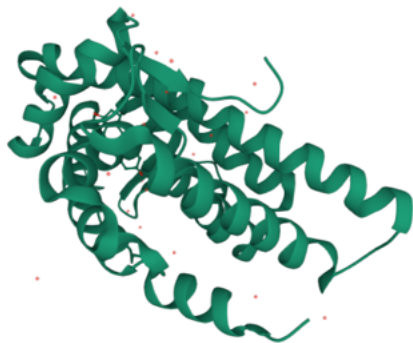
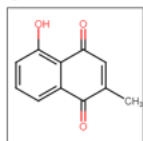


Figure 1

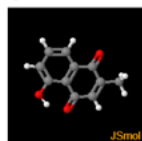
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Plumbagin

Ligand in 2D

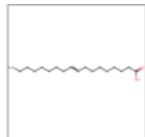


Ligand in 3D

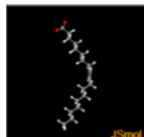


Oleic Acid

Ligand in 2D

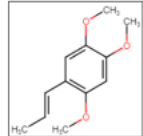


Ligand in 3D

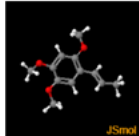


β -Asarone

Ligand in 2D

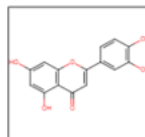


Ligand in 3D

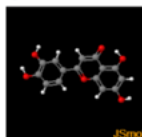


Lupeol

Ligand in 2D

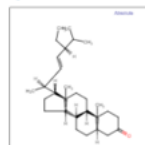


Ligand in 3D



Stigmasterol

Ligand in 2D



Ligand in 3D

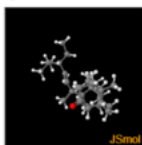


Figure 2

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