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MODULATION OF mTOR RECEPTOR IN DIABETIC NEPHROPATHY BY SANTALIN A OF LAL CHANDAN (*PTEROCARPUS SANTALINUS*): AN *IN-SILICO* ASSESSMENT BY MOLECULAR DOCKING

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Keywords:

Santalin-A, Diabetic nephropathy (DN), mTOR, *in-silico* molecular docking and Lalchandan, ADME, Druglikeness

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ABSTRACT: Background: Diabetic nephropathy (DN) is a primary cause of end-stage renal disease globally. Activation of mTOR and reduced autophagy has been identified as one of the pathogenic pathways. The presently available drugs have been successful in inhibiting the mTOR signaling, but show low oral bioavailability and suboptimal solubility. Rapamycin is a selective inhibitor of mTOR, shown significant protection against DN. However, its continuous use is associated with side effects. Thus, the search for novel drugs is on great demand. In the present study, *in-silico* approaches have been adopted to identify potential compounds with optimal oral bioavailability and better solubility properties, with no toxic effect. **Materials and Method:** The receptor protein mTOR with PDB ID: 3FAP was retrieved from the RCSB protein data bank. Total 20 compounds were selected from the list of 113, obtained from LC-MS of Lalchandan. Further, *in-silico* molecular docking calculation was done by using YASARA software. Drug-likeness and molecular property of best-docked compounds were checked by using Lipinski rule of five and Admet SAR server. **Result:** Five compounds showed interaction with mTOR protein. Out of these Santalin A showed the best interaction with binding energy 11.453[kcal/mol] and dissociation constant 4025.6841[pM]. Further, the Lipinski drug-likeness and admetSAR results also showed that Santalin A has good optimal oral bioavailability, non-carcinogenic and no toxic effect, suggesting all drug-like properties as compared to standard drug Rapamycin. **Conclusion:** Santalin-A, can be taken up as a potential lead compound for biological testing for developing a new drug for diabetic nephropathy, acting *via* mTOR signaling inhibition pathway.

INTRODUCTION: Bark / Heartwood of *Pterocarpus santalinus* (Family- Fabaceae) (PS) is already in clinical use in the Ayurvedic system of medicine. It is mainly found in Southern India and commonly known as 'Red Sanders.'

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Heartwood of PS has antipyretic, anti-inflammatory, anthelmintic, tonic, dysentery, hemorrhage, aphrodisiac, and diaphoretic activities [1]. It is also used in the treatment of diseases like bilious infections, skin diseases, eye diseases, ulcers and diseases related to blood [2, 3, 4].

It is also effective in inflammatory diseases such as chronic bronchitis, fever, chronic cystitis, mental aberrations, headaches, cancers, *etc.* [5, 6] Its major phytochemicals are santalin, pterolinus K and L, pterostilbenes, lupenone, dalbergia, Santalin-A, cearoin, Santalin B, sitosterol, betulin [7].

It mainly contains isoflavone glucosides and antitumor lignans like savinin and calocedrin [1]. Drinking of water twice a day in the cup of PS wood is in practice for treating diabetes [4, 8, 9]. Ethanol extract of stem-bark has been reported to have anti-hyperglycaemic activity [10]. However, its specific role in diabetic nephropathy is not well documented.

There is over-activation of mTOR in the kidney tissue of Diabetic nephropathy (DN). The DN is a progressive kidney disease triggered by demolition to the capillaries in the kidneys' glomeruli. It has two stages: micro-albuminuria and macro-albuminuria, its screening is made by measuring albumin in spot urine. An excess amount of protein/albumin secretion in the urine indicates glomerular damage [11]. The mTOR is a serine/threonine (S/T) protein kinase, of PI3K-related kinase family. It had unique sense ability towards nutrients availability, oxygen levels, cellular energy levels and mitogenic signals [12, 13], thus involved in controlling the cells growth, proliferation and metabolism and named as 'Master switch' [14, 15]. The mTOR is consists of the catalytic subunit of two basically distinct complexes, *i.e.*, mTORC1 and mTORC2. They have different sub-cellular partitions affecting their activation and function [16, 17]. There is involvement of mTOR in energy homeostasis by controlling the functioning of metabolic organs (liver, muscle, and adipose tissue). Deregulation of mTOR and its associated proteins leads to metabolic disorders like obesity, diabetes, and cancer [18].

The mTOR inhibitor includes Rapamycin, Temsirolimus, Everolimus, Deforolimus, Echino-mycin, *etc*. They may be specific or non-specific depending on their association with its intracellular receptor FKBP12 [19]. Rapamycin is a selective inhibitor of mTOR and has shown significant protection against DN. However, its continuous use is associated with side effects. The Rapamycin reacts with FKBP12, and this Rapamycin-FKBP12 complex directly interacts to the FKBP12-Rapamycin Binding (FRB) domain of mTOR, inhibiting its activity [20]. However, being potent, Rapamycin shows low oral bioavailability and suffers solvent solubility concerns. So there is a need for searching the new potential compound for overcoming the drawbacks of Rapamycin for inhibiting mTOR. In the present study, the interaction of different phytochemicals of Lalchandan with mTOR protein has been studied and compared with standard drug Rapamycin.

MATERIALS AND METHODS:

Retrieval of Protein Structure and Active Site Prediction: Based on the literature survey, it has been reported that mTOR can be used as a prominent receptor for structure-based drug designing. The three-dimensional structure of mTOR protein with PDB ID-3FAP was retrieved from RCSB Protein Data Bank (http://www.rcsb.org). The Protein receptor preparation was performed out by optimizing protein model geometry, removal of ligands and other heteroatoms using the Discovery studio 3.0 [21]. Further, the protein model was used for the active site prediction using Discovery studio 3.0 and MetaPocket. The meta pocket is a meta approach to improve protein-ligand binding site prediction (http://metapocket.eml.org) [22].

Ligand Selection: Out of screened 113 compounds, obtained through LC-MS (Liquid Chromatography-Mass Spectroscopy) of *Pterocarpus santalinus* (Lalchandan) only 20 bioactive compounds were selected based on DB (database) difference in ppm. LC-MS of the aqueous extract of the plant was performed at IIT Pawai, Mumbai, India. The 2D structures of selected ligands were retrieved in SDF format by using the PubChem compound database (http://pubchem.ncbi.nlm.nih.gov/). All retrieved compounds were further converted into 3D PDB format using Discovery Studio 3.0. Further, energy minimization and ligand optimization were also carried out using Discovery Studio 3.0.

Molecular Docking and Assessment: For molecular docking, YASARA software was used [23]. Using YASARA, selected 20 phytochemicals were docked with mTOR protein (PDB ID: 3FAP). In YASARA, receptor and ligand files were used to set a target and play the macro. The macro file dockrun_mcr was used to calculate the interaction between the receptor and selected ligands individually. Further objects files (docked complexes) were visualized using YASARA software and converted in PDB files for 2D-3D interaction using Discovery studio 3.0. The result

log files obtained from YASARA was used for docking calculation. The docking runs were sorted by binding energy [kcal/mol] and dissociation constant [pM]. The compounds with more positive binding energy showed stronger interaction.

Druglikeness and Molecular Property Prediction: The top selected phytochemicals, based on binding energy [kcal/mol] and dissociation constant [pM], were taken for drug-likeness by using Lipinski filter (http://www.scfbioiitd.res.in/software/drugdesign/lipinski.jsp) [24, 25]. The molecular property, absorption, distribution, metabolism, excretion, and toxicity prediction was calculated by the admetSAR server (A Comprehensive server for Assessment of Chemical ADMET Properties; http://lmmd. ecust.edu.cn:8000/about/) [26].

RESULT AND DISCUSSION:

Retrieved Protein Structure and Predicted Active Site: To identify the suitable drug, mTOR protein was selected for *in-silico* interaction study. The predicted model of mTOR protein (PDB ID: 3FAP) was retrieved from RCSB protein data bank, and receptor protein was prepared by using Discovery studio 3.0. The retrieved and prepared protein structure of mTOR was visualized using YASARA view **Fig. 1**. The stereochemical quality of protein structure coordinates was checked using RAMPAGE and PDBSum server and found good stereochemical quality for selected mTOR protein model.

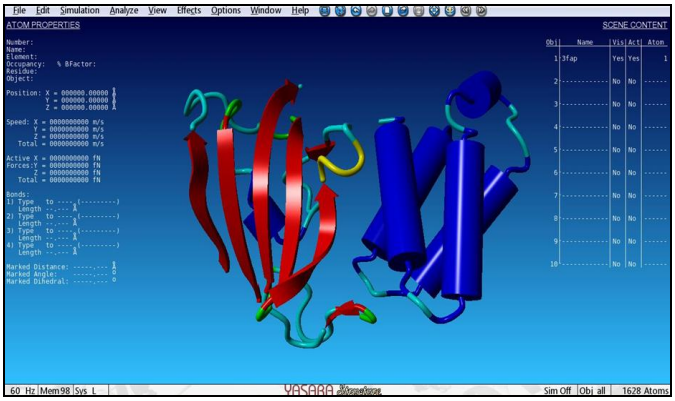
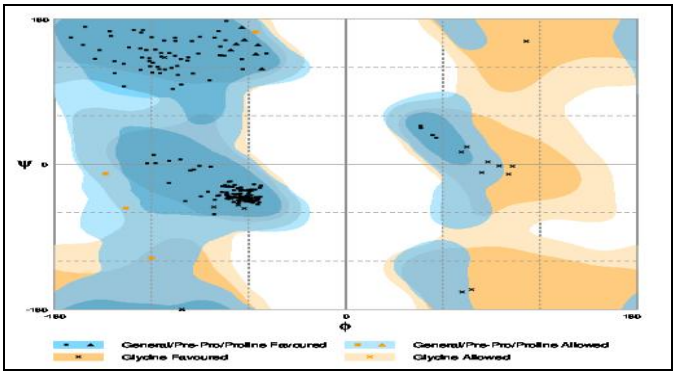
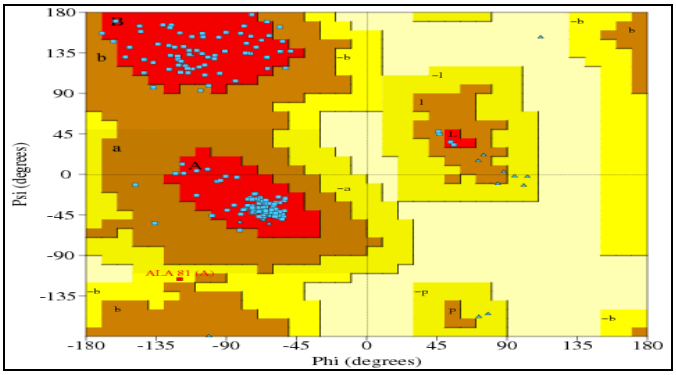


FIG 1: THE mTOR PROTEIN MODEL (PDB ID: 3FAP) VISUALIZED USING YASARA SOFTWARE. RED COLOR INDICATES BETA SHEET, BLUE HELICES, GREEN COIL AND CYAN COLOR INDICATES TURNS

Evaluation of residues was performed using RAMPAGE, and 98.0% residues were found in the favoured region (~98.0% expected), while 2.0% residues were observed in the allowed region (~2.0% expected) and no residue was in outlier region **Fig. 2a** [27].





Evaluation of residues

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Residue [A  13 :ARG] (-148.24, -11.74) in Allowed region
Residue [A  56 :ILE] ( -55.75, 163.75) in Allowed region
Residue [A  81 :ALA] (-119.90,-116.33) in Allowed region
Residue [A  90 :ILE] (-135.81, -54.42) in Allowed region
Number of residues in favoured region    (~98.0% expected)  :  193 ( 98.0%)
Number of residues in allowed region     ( ~2.0% expected)  :    4 (  2.0%)
Number of residues in outlier region                        :    0 (  0.0%)
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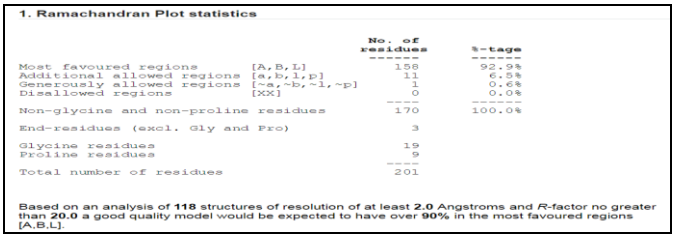
FIG. 2A: STEREOCHEMICAL QUALITY OF PROTEIN STRUCTURE COORDINATE OF mTOR PROTEIN MODEL (PDB ID: 3FAP) BY RAMPAGE SERVER. DARK BLUE COLOR INDICATES GENERAL/PRE-PRO/PROLINE FAVOURED REGION, LIGHT BLUE GENERAL/PRE-PRO/PROLINE ALLOWED REGION, DARK ORANGE GLYCINE FAVOURED REGION AND LIGHT ORANGE INDICATES GLYCINE ALLOWED REGION



1. Ramachandran Plot statistics

		No. of residues	%-tage
Most favoured regions	[A,B,L]	158	92.9%
Additional allowed regions	[a,b,l,p]	11	6.5%
Generously allowed regions	[~a,~b,~l,~p]	1	0.6%
Disallowed regions	[XX]	0	0.0%
Non-glycine and non-proline residues		170	100.0%
End-residues (excl. Gly and Pro)		3	
Glycine residues		19	
Proline residues		9	
Total number of residues		201	

Based on an analysis of **118** structures of resolution of at least **2.0** Angstroms and *R*-factor no greater than **20.0** a good quality model would be expected to have over **90%** in the most favoured regions [A,B,L].

FIG. 2B: RAMACHANDRAN PLOT STATISTICS OF mTOR PROTEIN (PDB ID: 3FAP) BY PDBSUM SERVER. COLOR RED INDICATES LOW-ENERGY REGIONS, YELLOW ALLOWED REGIONS, PALE YELLOW THE GENEROUSLY ALLOWED REGIONS, AND WHITE DISALLOWED REGIONS (COLOR FIGURE ONLINE)

Another server PDBsum was also used for Ramachandran plot statistics calculation. Based on this server 92.9% residues were observed in most favoured regions [A,B,L], 6.5% in additional allowed regions [a,b,l,p], 0.6% residues in generously allowed regions [~a,~b,~l,~p] while no residues were found in disallowed regions. For a good quality model, it would be estimated to have over 90% in the most favored regions [A, B, L] **Fig. 2b** [28]. Further, the prominent active site was identified using Discovery Studio 3.0.

Ligand Details and their Retrieval: Ligands from water extract of LC-MS (Liquid Chromatography-Mass Spectroscopy) of *Pterocarpus santalinus* (Lalchandan) wood powder, were taken by their DB (database) (ppm) difference whose higher concentration showed good bio-availability and excellent absorption. The 2D-structure of selected phytochemicals was retrieved from PubChem compound database in SDF format.

Further, the protein geometry of these phytochemicals was prepared and converted in 3D PDB format using Discovery studio 3.0. After conversion, these phytochemicals were taken for docking calculation. Out of this 20 phyto-chemicals only 5 compounds namely santalin A, santalin B, sitosterol, lupeol, and betulin were selected by binding energy and dissociation constant (described below) **Table 1**. Structures of these compounds were shown in **Fig. 3**.

Out of these 5 compounds, Santalin A showed more positive binding energy and dissociation constant with mTOR protein. The binding energy of Santalin A was equivalent to the binding energy of standard drug Rapamycin. There is a minute difference in their binding energies **Table 1**. Further, the drug-likeness and molecular property ADMET were checked for this compound and compared with standard drug Rapamycin (described below) **Table 2**.

TABLE 1: DOCKING CALCULATION DETAILS OF STANDARD RAPAMYCIN AND OTHER PHYTOCHEMICALS OF LALCHANDAN WITH mTOR PROTEIN (PDB ID: 3FAP)

Ligand Used	Bind. Energy [kcal/mol]	Dissoc. constant [pM]	Contacting receptor residues
Rapamycin	12.943	325.5781	TyrA^{26}, PheA^{36}, AspA^{37}, ArgA^{42}, PheA^{46}, LysA^{52}, GlnA^{53}, GluA^{54}, ValA^{55}, IleA^{56}, TyrA^{82}, HisA^{87}, IleA^{90}, LeuB^{13}, GluB^{14}, SerB^{17}, ArgB^{18}, PheB^{21}, GlyB^{22}, ArgB^{24}, LysB^{77}, ThrB^{80}, TrpB^{83}, AspB^{84}, TyrB^{86}, TyrB^{87}, PheB^{90}
Santalin A	11.453	4025.6841	TyrA^{26}, PheA^{36}, AspA^{37}, PheA^{46}, ValA^{55}, IleA^{56}, TrpA^{59}, TyrA^{82}, HisA^{87}, IleA^{90}, IleA^{91}, PheA^{99}, LeuB^{120}, SerB^{124}, PheB^{128}, LysB^{184}, ThrB^{187}, TrpB^{190}, AspB^{191}, TyrB^{193}, TyrB^{194} , PheB^{197}
Santalin B	11.129	6955.604	TyrA^{26}, PheA^{36}, AspA^{37}, PheA^{46}, ValA^{55}, IleA^{56}, TrpA^{59}, TyrA^{82}, HisA^{87}, IleA^{90}, IleA^{91}, PheA^{99}, LeuB^{120}, GluB^{121}, SerB^{124}, PheB^{128},LysB^{184},ThrB^{187}, TrpB^{190}, AspB^{191}, TyrB^{193}, TyrB^{194}
Sitosterol	11.068	7709.8945	TyrA^{26}, PheA^{36}, AspA^{37}, PheA^{46}, GluA^{54}, TyrA^{82}, IleA^{90}, LeuB^{120}, GluB^{121}, SerB^{124}, PheB^{128}, LysB^{184}, ThrB^{187}, TrpB^{190}, AspB^{191}, TyrB^{194}, PheB^{197}
Lupeol	11.031	8206.7236	TyrA^{26}, AspA^{37}, PheA^{46}, GlnA^{53}, GluA^{54}, TyrA^{82}, GluB^{121}, SerB^{124}, ArgB^{125}, PheB^{128}, ThrB^{187}, TrpB^{190}, AspB^{191}, TyrB^{194}, PheB^{197}
Betulin	10.227	31879.3613	TyrA^{26}, AspA^{37}, ArgA^{42}, PheA^{46}, GlnA^{53}, GluA^{54}, GluB^{121}, SerB^{124}, ArgB^{125}, PheB^{128}, GlyB^{129}, ThrB^{187}, TrpB^{190}, AspB^{191}, TyrB^{194}, PheB^{197}

TABLE 2: DRUGLIKENESS AND MOLECULAR PROPERTY PREDICTION FOR BOTH RAPAMYCIN (CID: 5284616) AND SANTALIN A

Properties	Rapamycin (CID: 5284616)	Santalin A (CID: 5490179)
Molecular mass	902.000000	584.000000
Hydrogen bond donor	7	5
Hydrogen bond acceptor	13	10
Log p	4.275319	5.494692
Ames test	Non AMES toxic	Non AMES toxic
Carcinogenity	Non-carcinogens	Non-carcinogens
Human intestinal absorption	HIA-	HIA+

Docking Calculation: In molecular docking calculation, human FKBP12 and FRB domain of mTOR protein (PDB ID: 3FAP) structure were taken. The 20 bioactive compounds were selected for docking with FKBP12 and FRB domain of mTOR protein using YASARA software.

Two different approaches are presently available: 1. Autodock and 2.VINA. The Autodock is a highly quoted docking program developed at the Scripps Research Institute by Dr. Garrett M. Morris et al. [29]. VINA has also been established at the Scripps Research Institute, by different authors, Dr. Oleg Trott and Dr. Arthur J. Olson [30]. From the literature survey, it has been found that Rapamycin is the first inhibitor of mTOR protein [31] so in the present study, it has been adopted as a standard drug for docking calculation. In docking calculation, Rapamycin shows similar results as obtained by X-ray diffraction method. In this PDB file, C15- (R)- Methylthienyl Rapamycin (Rapamycin analog) is reported in complex with both human FKBP12 and FRB domain of FRAP [32].

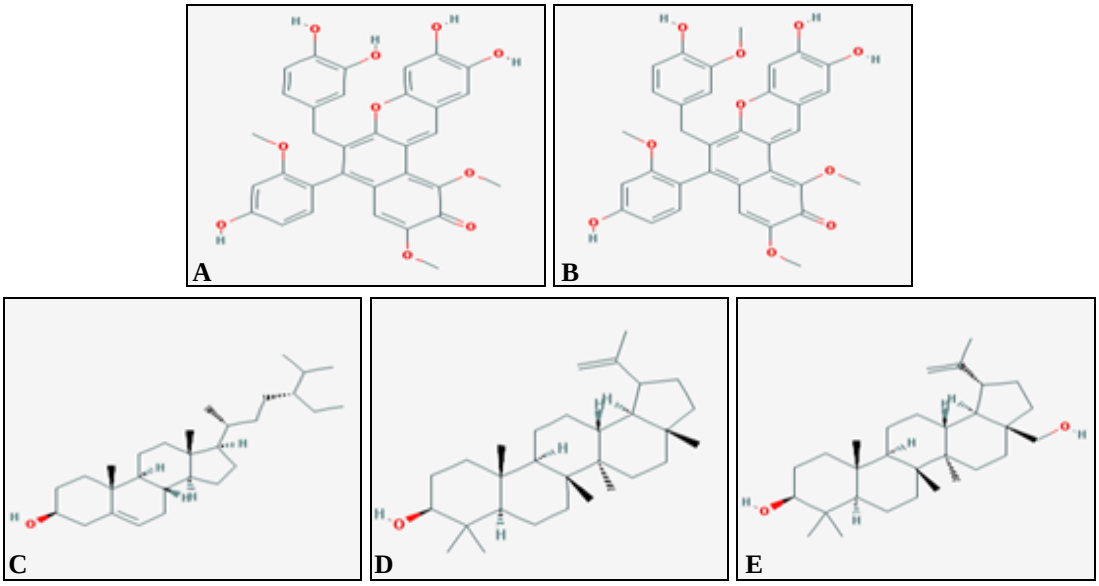


FIG. 3: STRUCTURE OF DIFFERENT PHYTOCHEMICALS FROM PS (A) SANTALIN A, (B) SANTALIN B, (C) SITOSTEROL, (D) LUPEOL AND (E) BETULIN

After docking calculation, the result log files were generated for all 20 selected compounds. The first docked cluster was taken for all selected compounds by binding energy [kcal/mol] and dissociation constant [pM]. Out of 20 selected compounds, it has been observed that only five compounds namely santalin A, santalin B, sitosterol, lupeol, and betulin showed interaction. Out of these Santalin A (CID: 5490179) showed the best interaction with binding energy 11.453 [kcal/mol] and dissociation constant 4025.6841 [pM] with mTOR protein **Table 1**. After clustering the 25 runs, 15 distinct complex conformations were found for Santalin A. They all differ by at least 5.0 A heavy atom RMSD. Further, the best-docked compound Santalin A was taken for interactive visualization using Discovery studio 3.0. The hydrogen bonding and hydrophobic interaction were shown in **Fig. 4a-b**.

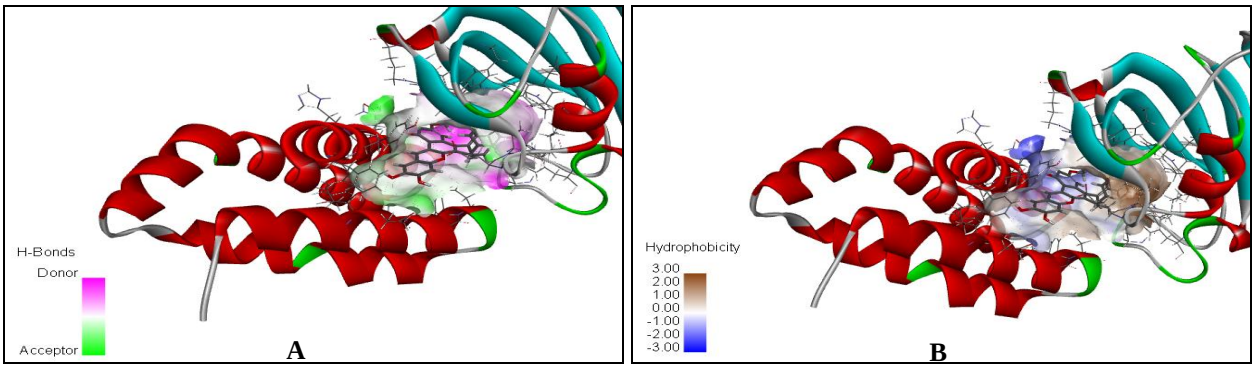


FIG 4: (A) HYDROGEN BONDING, AND (B) HYDROPHOBICITY, OF SANTALIN A WITH mTOR PROTEIN

The 2D-3D interaction involves the active site amino acid residues TyrA[26], PheA[36], AspA[37], PheA[46], ValA[55], IleA[56], TrpA[59], TyrA[82], HisA[87], IleA[90], IleA[91], PheA[99], LeuB[120], SerB[124], PheB[128],

LysB[184], ThrB[187], TrpB[190], AspB[191], TyrB[193], TyrB[194] and PheB[197] of mTOR with Santalin A **Fig. 5a-b**. The residues PheA[46], TyrA[82] and PheB[128], showed Pi-Pi interaction, and the residue IleA[56] showed direct interaction with Santalin A. The more positive binding energy of Santalin A as compared to other phytochemicals of PS (Lalchandan) showed strongest interaction with mTOR protein and equivalent interaction with standard drug Rapamycin. From literature survey, it has been found that phytochemical, Santalin A is a red pigment found in PSWE, but its direct interaction and positive binding affinity towards mTOR protein showed that it could be used as a drug for various metabolic syndromes including DN.

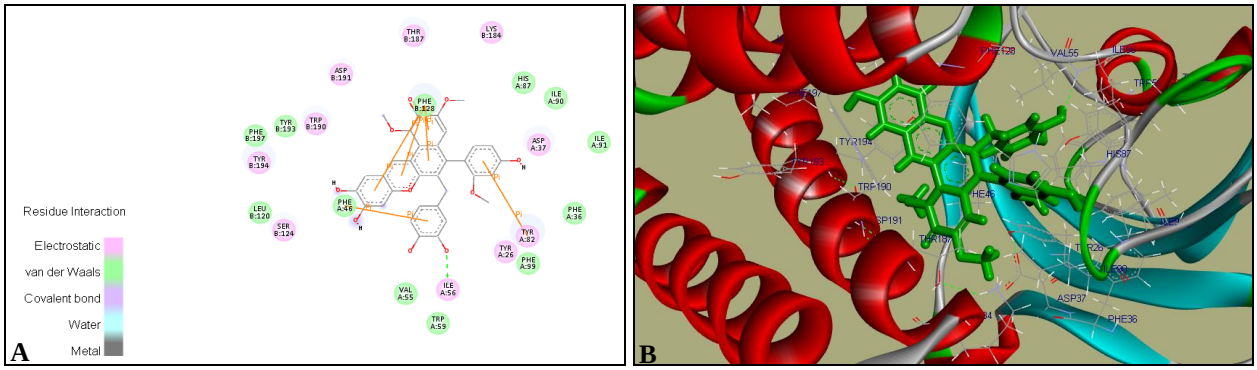


FIG. 5: (A) 2D INTERACTION OF SANTALIN A WITH mTOR PROTEIN-ALL THE RESIDUES IN PINK COLOR SHOWS ELECTROSTATIC INTERACTION, AND GREEN COLOR SHOWS VAN DER WAALS INTERACTION. THE RESIDUES PHEA46, TYRA82AND PHEB128 SHOWES PI-PI INTERACTION WITH SANTALIN; (B) 3D INTERACTION OF SANTALIN A WITH mTOR PROTEIN

Druglikeness and ADMET Profile Analysis: Further, the drug-likeness and molecular property, absorption, distribution, metabolism, excretion, and toxicity profiles were checked for standard Rapamycin and Santalin A. The drug-likeness analysis using Lipinski filter showed that Santalin A following all properties (Molecular mass, Hydrogen bond donor, Hydrogen bond acceptor, Log P, and Molar refractivity) in comparison with Rapamycin **Table 2**.

The molecular property profile results also indicate positive sign towards human intestinal absorption (HIA) ensuring that the Santalin A passes human intestinal absorption (HIA) models and have no AMES toxic and carcinogenic effects **Table 2** [33]. The comparative analysis showed that Santalin A could be a better drug in comparison to other selected phytochemicals of Lalchandan and standard drug Rapamycin.

CONCLUSION: The docking study of 20 selected compounds of Lalchandan concluded that Santalin A showed good binding energy (11.453kcal/mo]) and dissociation constant (4025.6841pM) with mTOR protein. The contacting receptor residues TyrA[26], PheA[36], AspA[37], PheA[46], ValA[55], IleA[56], TrpA[59], TyrA[82], HisA[87], IleA[90], IleA[91], PheA[99], LeuB[120], SerB[124], PheB[128], LysB[184], ThrB[187], TrpB[190], AspB[191], TyrB[193], TyrB[194], and PheB[197]of mTOR protein were involved in interaction with Santalin A. Further, the Lipinski rule and admetSAR results also justify Santalin-A, as a potential drug, because of its better solubility, optimal oral bioavailability, non-carcinogenic response and other non-toxic effects as compared to standard drug Rapamycin.

Thus, it can be considered a a better inhibitor for mTOR protein in comparison to Rapamycin and other phytochemicals. Thus it could be concluded that Santalin A can be used as a potential lead compound for drug development against different metabolic disorder including Diabetic nephropathy.

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CONFLICT OF INTEREST: Authors declare that there is no conflict of interest.

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