Beni-Suef University Journal of Basic and Applied Sciences

RESEARCH

Open Access

In silico screening and molecular docking study of compounds from *Pedalium murex* L. with Vasopressin2 receptor target for Autosomal Dominant Polycystic Kidney Disease

Gobind Ram[1,2], Anil Kumar[3], Hemlata[1], Gulab Singh[1] and Shiv Kumar Giri[1*]

Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is frequently inherited disease. The medicinal plant *Pedalium murex* (*P. murex*) Linn, that has anti-inflammatory, antiurolithiatic, and diuretic properties, has a greater tendency to cure urinary defects. *P. Murex* compounds have been studied in order to find an effective treatment against the Vasopressin 2 receptor (V2R), which is a target for ADPKD. The compound structures were designed using ChemSketch software, which was then optimised for the exploration of pharmacokinetic properties. Finally, AutoDock VINA programme was used to execute molecular docking, and the findings were analysed and visualised in Discovery studio visualizer.

Results: Virtual screening using PyRx software finds seven compounds from *P. murex* with binding affinities ranging from −8.6 to −5.8 kcal/mol, which will be used for further pharmacological characteristics study. Luteolin has a higher druglikeness and an overall drug score of 0.84, indicating as a most suitable compound. Furthermore, luteolin docking and bonding study reveals improved receptor (V2R) H-bonding with Phe105(2.26 and 2.96), Gln119(2.78), and any Lys116(2.16).

Conclusions: Based on affinity score, screening of various compounds from *P. murex* against the V2R target for the ADPKD showed that the phytocompound luteolin has superior pharmacological characteristics and bonding. Luteolin from *P. murex* can be used as a possible therapeutic candidate after rigorous in silico investigation.

Keywords: Polycystic kidney disease, Drug likeness, Binding affinity

1 Background

A number of abnormal signalling pathways become triggered in autosomal dominant polycystic kidney disease (ADPKD), resulting in renal cytogenesis [1]. Polycystin-1 (PC1) and Polycystin-2 (PC2) encoded by *PKD1* and *PKD2* genes that work as a complex in the normal renal architecture, gets affected and become non-functional by binding of Gα-subunit of GPCR at G-protien binding site of PC1 that subsequently activates number of aberrant signalling pathways. The sodium/potassium/chloride co-transporter, i.e. SLC12A1 (encodes NKCC2), which is found in the apical membrane of the thick ascending loop of henle (TAL), plays an important role in renal function and is regulated by the Vasopressin2 receptor(V2R) protein [2]. To regulate the passage of ions into and out of renal cells, the cross talks of SLC12A1 among other renal transporters proteins play important role for normal kidney functions [3]. Vasopressin levels increase in disease, and abnormally high intracellular cyclic AMP (cAMP)

*Correspondence: goswamishiv@gmail.com
[1] Department of Biotechnology, School of Basic and Applied Sciences, Maharaja Agrasen University, Baddi (Solan), Himachal Pradesh, India
Full list of author information is available at the end of the article

Table 1 Compound screening from Pedalium *murex L*

S. nos.	Plant part	Name of the compound	Binding energy	Pub-Chem-ID
1	Leaves	Diosmetin	−8.6	CID = 5281612
2	Fruits	Luteolin	−8.5	CID = 5280445
3	Leaves and flowers	Hispidulin	−8.2	CID = 5281628
4	Fruits	Caffeic acid	−8.0	CID = 750
5	Flower	Quercetin	−7.7	CID = 5280343
6	Stem	Saponins	−7.6	CID = 6540709
7	Leaves	Vanillic acid	−5.8	CID = 8468

Seven compounds with binding energies between −8.6 and −5.8 kcal/mol have been shortlisted on the docking-based screening using PyRx software

levels cause an imbalance in the SLC12A1, a Na:K:Cl co-transporter, resulting in a reduction in calcium levels and chloride secretion from cyst lining [4]. The Vasopressin 2 receptor is impaired as the amount of cAMP increases in a disease state, which affects nephronal reabsorption, resulting in a urinary defect [5]. cAMP plays a central role in the pathogenesis of ADPKD. The tolvaptan drug has several renal and extrarenal side effects [6]. Different amino acids involved in ligand binding have been identified and used in a molecular docking study against a *P. Murex* compound.

P. Murex (Family: Pedaliaceae) is a commonly known as Large Caltrops or Gokhru (India). Different parts of plant are used for the treatment of different ailments. It has a high proclivity for curing deadly diseases due to its anti-inflammatory, antiurolithiatic, and diuretic properties, as well as a high tendency for curing urinary defects. Complications such as urinary tract disease and gastrointestinal tract disorders have also been benefited [7]. Pharmacologically, *P. murex* has been investigated for antiulcerogenic, nephroprotective, hypolipidemic, aphrodisiac, antioxidant, and antimicrobial activities. The existence of a significant amount of compounds used for the synthesis of contraceptic drugs has made the plant famous among phyto-chemists [8]. Quercetin, diosmetin, luteolin, hispidulin, ursolic acid, caffeic acid, and various fatty acids are among the other phytochemicals contained in the plant [9].

The recent research has focused on identifying a possible ligand molecule from *P. Murex,* which can act as a suitable drug candidate. The compounds from *P. murex* were identified using docking-based screening, drug properties, molecular docking, and further bonding with V2R was identified to finalise the suitable complex for the treatment of ADPKD.

2 Methods

Compounds from *P. murex* have been identified, designed, optimised, and screened using docking to determine the most suitable natural compound that can inhibit V2R. Because its functionality is affected as a result of improper signalling, which affects the renal transporters as previously discussed, the V2R protein is a possible target protein in ADPKD.

2.1 Receptor structure identification

The sequence of the vasopressin V2 receptor isoform 1 (*Homo sapiens*) is retrieved from NCBI's GenBank. The structure of the vasopressin V2 receptor isoform 1 (*Homo sapiens*) is predicted by Swiss-Model, an automated modelling server, by using the best template identified by the sequence alignment based on the expected value and scores. The atom coordinate file of the template structure is retrieved from PDB (Protein Data Bank) database. Predicted structure is then visualised, and energy is minimised using SwissPDBViewer (SPDBV), a structure visualization and analysis tool [10]. Further, properties of the receptor are identified and validated by PROCHECK structure validation tool.

2.2 Binding/active site identification

In order to identify amino acids involved in receptor binding, a SCFBIO Tool (http://www.scfbio-iitd.res.in/) was used for the prediction of putative active site. The amino acids Val115, Lys116, Gln119, Met123 have been involved in the receptor binding and responsible for key functionality as per literature search [11, 12]. By targeting these amino acids, an aberrant signalling can be reduced or stopped. The active site/binding site dimensions were selected according to amino acids involved in receptor binding.

2.3 Compounds screening

The compound from *P. murex* was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the chemical structure was drawn by ChemSketch software (ACD/Labs Version 2020.2.1) [13]. Further, open babel software (Version 3.1.1) has been used to convert molecular file formats of compounds [14]. The library of ligand molecules was then subjected to virtual screening based on docking using PyRx software [15]. PyRx classified the ligands according to their binding affinity, which represents the highest potential interaction with the receptor. The molecules with the lowest binding affinity (Kcal/mol) were chosen for further investigation of drug properties.

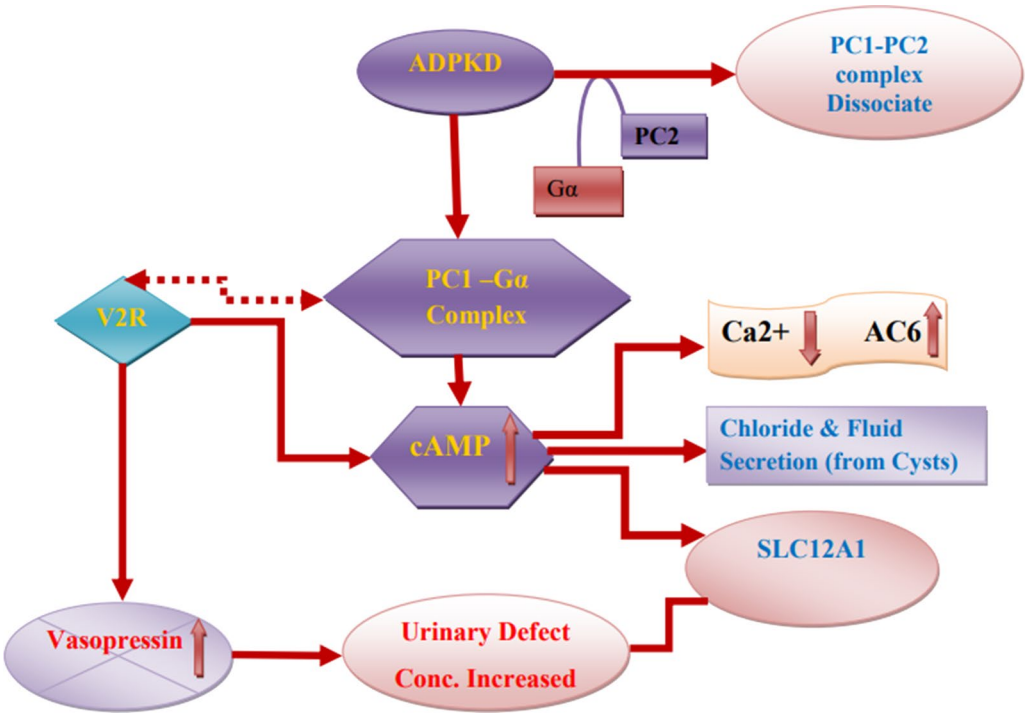

Fig. 1 Vasopressin2 receptor signalling in autosomal dominant polycystic kidney disease. Dissociation of polycystin complex (PC1 and PC2) and binding of Gα subunit of GPCR with PC1 subsequently leads to the aberrant increase in the level of cAMP. The pathogenic activation of the Vasopressin2 receptor causes an abnormal increase in vasopressin levels, as well as an increase in cAMP levels. Cyclic AMP (cAMP)-driven mechanisms are central to the pathogenesis of ADPKD. It affects the functionality of SLC12A1 renal transporter, i.e. a regulator of Na:K:Cl co-transporter

2.4 Drug properties identification

The pharmacological properties of the ligand molecules were identified by OSIRIS properties explorer [16–18]. The lipinski's rule, molecular weight, H- bond acceptor, H-bond donor, clogp, druglikeness and drug score were analysed. The above-mentioned software was also used to investigate their mutagenic, tumorigenic, irritating, and reproductive effects. The compounds were then studied for molecular weight, clogp, topological polar surface area (TPSA), solubility, H-donor, H-acceptor, druglikeness, and total drug score. The software employed the logarithm of the partition coefficient between n-octanol and water, log(Coctanol/Cwater), to calculate compound hydrophilicity. Because high values imply poor absorption, substances with a clogp value of less than 5.0 have a high possibility of being well absorbed.

Table2 Properties of the selected compounds as a drug candidate

S. nos	Compound	Mol weight (g/mol)	clogp	TPSA	Solubility	H-donor	H-acceptor	Druglikeness	Drug score
1	Diosmetin	300	2.27	96.22	− 2.87	3	6	2.07	0.83
2	Hispidulin	300	2.27	96.22	− 2.87	3	6	1.11	0.77
3	Luteolin	286	1.99	107.2	− 2.56	4	6	1.9	0.84
4	Quercetin	302	1.49	127.4		5	7	1.6	0.3
5	Caffeic acid	180	0.78	77.76	− 1.41	3	4	1.62	0.19
6	Vanillic acid	168	0.73	66.76	− 1.35	2	4	− 1.31	0.35
7	Saponins	1130	− 0.7	388	− 4.87	12	24	− 10.72	0.12

Properties of the selected natural compounds show that diosmetin, hispidulin, and luteolin show better drug properties, whereas luteolin with molecular weight 286 g/mol shows best properties as compared to other compounds

Table 3 Types of bonding and interacting amino acids of V2R with top five compounds

S. nos	Name of the compound	Binding energy	H-bonding	Vander wall	Pi-alkyl	Pi-Pi stacked	Unfavourable acceptor-acceptor
1	Diosmetin	− 8.6	GLN-96	CYS-192	ALA-98, PRO-95	PHE-105	GLN-119
2	Luteolin	− 8.5	PHE-105, GLN-119, LYS-116	–	CYS-192, ALA-98, PRO-95	–	GLN-96
3	Hispidulin	− 8.2	–	ARG-106	ALA-98, PRO-95, CYS-192	PHE-105	–

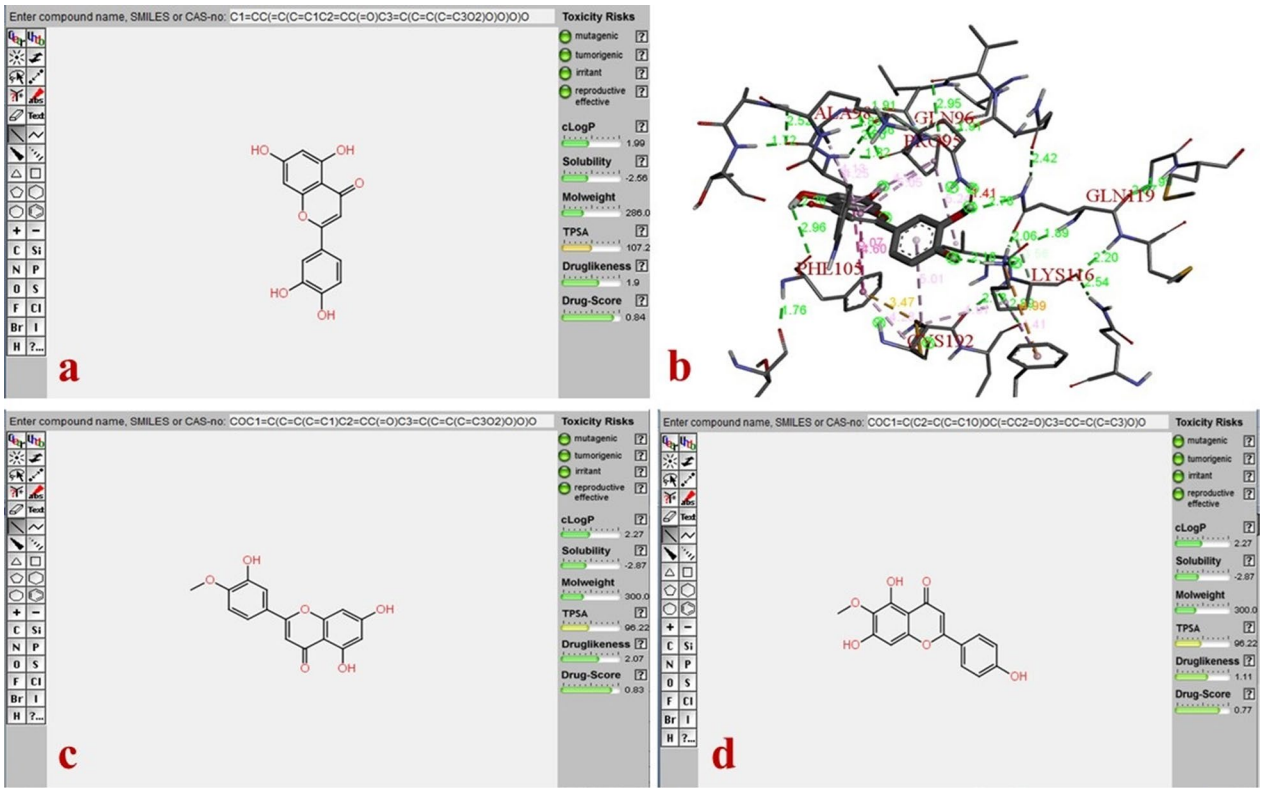

Fig. 2 Comparative study of luteolin, diosmetin and hispidulin and luteolin interaction with V2R target. **a** Luteolin good overall drug score (0.84) with no toxicity. **c** Diosmetin shows 0.83 overall drug score **d** Hispidulin shows 0.77 overall drug score. **b** shows conventional H-bonding with PHE105, GLN-119, LYS-116

Drug absorption, including intestinal absorption, bioavailability, and blood–brain barrier penetration, has been identified by topological polar surface area (TPSA). It is a valuable measure for predicting drug transport characteristics. A compound's water solubility has a considerable impact on its absorption and distribution characteristics. Low solubility is usually associated with poor absorption; therefore, the overall goal is to avoid poorly soluble compounds.

2.5 Docking verification and analysis

The shortlisted ligand molecule based on the drug properties and docking potential is again verified by AutoDock VINA. In addition, the discovery studio visualizer is used to visualise and analyse the shortlisted docked complexes [19]. AutoDock VINA is a versatile molecular docking software that offers nine different docked ligand molecule modes with the receptor. The optimal mode with the lowest binding energy was chosen and studied

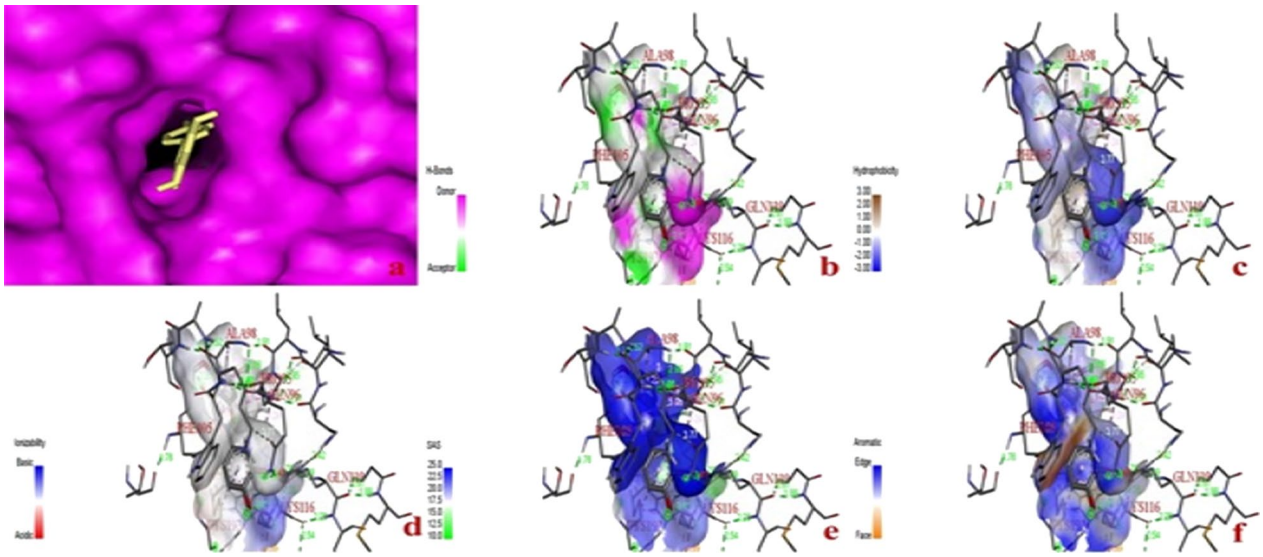

Fig. 3 Luteolin docking with V2R and cavity properties.. **a** PyMol docked view. **b** cavity H-bond view. **c** Cavity hydrophobicity view. **d** Cavity ionizability view. **e** Show good solvent accessibility. **f** Aromaticity View

for various bonding distances and interactions with the binding site residues.

3 Results

The V2R amino acids that have a proclivity for binding ligand molecules were found through the literature search mentioned earlier (Fig. 1). Dissociation of polycystin complex (PC1 and PC2) subsequently leads to the aberrant increase in the level of cAMP. The pathogenic activation of the Vasopressin2 receptor causes an abnormal increase in vasopressin levels, as well as an increase in cAMP levels. Cyclic AMP (cAMP)-driven mechanisms are central to the pathogenesis of ADPKD. It affects the functionality of SLC12A1 renal transporter, i.e. a regulator of Na:K:Cl co-transporter. The vasopressin V2 receptor isoform 1 (*Homo sapiens*) sequence was obtained from NCBI's GenBank (accession number: NP_000045.1), and homology modelling was performed using Swiss-Model with the best match template selected from a BLAST search against the (Protein Data Bank) PDB database, and energy was minimized by steepest Descent and Conjugate gradient methods. PROCHECK analysed the expected model and found 91 per cent core value.

3.1 Active site prediction

SCFBio Tools (http://www.scfbio-iitd.res.in/) predicted the V2R active site and correlated the results with the literature reference. For the binding site identification, chosen amino acids with putative roles in functionality and aberrant signalling were investigated. The selected cavity points of the predicted site of docking were −11.372, −4.173, 101.662, and the cavity volume is 457 Å cubic (Cavity5 = LRNVAGWHFPSMYITC). Based on the selected amino acids, the cavity dimensions further used for docking-based screening.

3.2 Ligand designing and virtual screening

ChemSketch (ACD/Labs Version 2020.2.1) was used to design the structure of natural *P. murex* compounds, which were stored in.mol2 format, and all of the chemical structures were translated from.mol2 to.pdb format using Open Babel Software (Version 3.1.1). PyRx software was used to screen a library of lignad molecules in pdb format for docking-based screening with V2R as the target protein. In the configuration file for the PyRx software's AutoGrid engine, the grid box dimension (Å) X = −11.8561 Å, Y = 4.4132 Å, Z = 122.1596 Å was used. Compounds with binding energy ranging from −8.6 to −5.8 kcal/mol were selected for further analysis (Table 1).

3.3 Pharmacokinetic properties of the selected ligands

The ADMET analysis of the selected compound reveals that diosmetin and hispidulin shows 0.83 and 0.77 overall drug score with molecular weight 300 g/mol. Among the other natural compounds investigated, luteolin had the lowest molecular weight 286, clogp 1.99, solubility −2.56, druglikeness score 1.9, and overall best drug score of 0.84. Due to the druglikeness, cLogp, solubility, molecular weight, and toxicity risks, the drug score displays a

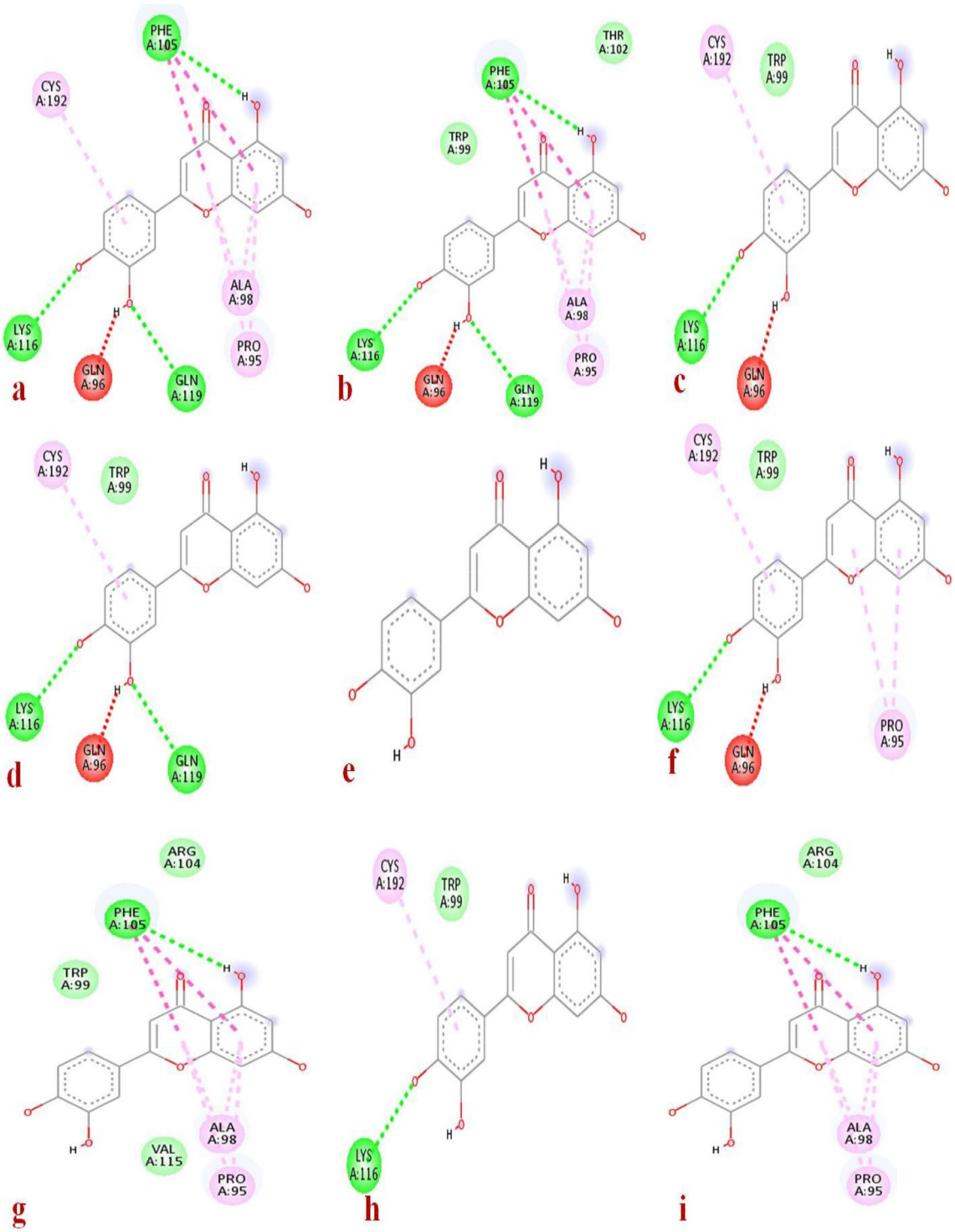

Fig. 4 Interaction representation of V2R with luteolin. H-bonding Van der Walls Interaction Pi-Cation Pi-Pi Stacked Alkali Pi-Sulphur . Conventional H-bonding with bond distance PHE105, GLN-119, LYS-116

compound's overall frequency to qualify as a drug candidate. Furthermore, the examination reveals no toxicity and follows the Lipinski rule as shown in Table 2.

On the basis of ADMT analysis, diosmetin, hispidulin and luteolin docking are again verified by AutoDock VINA with the same grid dimension and visualized in UCFS Chimera [20]. For the bonding and interaction analysis, complexes were subjected to discovery studio visualized for the bonding interaction analysis. Diosmetin shows H- bonding with GLN-96, Vanderwall interaction with Cys192 and Pi-Alkali bonding with Ala98 & Pro95 amino acids of V2R, whereas luteolin shows H-bonding with Phe105, Gln-119 and Lys-116 and Pi-Alkali bonding with Cys192, Ala98, Pro95. The hispidulin only shows vanderwall Arg106 and Pi-Alkali interaction with Ala98, Pro95 and Cys192 as shown in Table 3. Luteolin form conventional H-bonding with the amino acids is involved in the ligand binding within the predicted active site (Fig. 2). Further, luteolin docking with V2R is again verified, and interaction pattern is studied as shown in Fig. 3, and further bonding analysis reveals better receptor (V2R) H-bonding with Phe105(2.26 and 2.96 Å), Gln119(2.78 Å) and Lys116(2.16 Å) residues involved in receptor binding (Fig. 4).

4 Discussion

Compounds from medicinal plant *P. murex* were analysed and docked with V2R in order to identify the best complex that can be further analysed in vitro study. *P.murex* has nephroprotective activity [21]. cAMP plays a key role in the pathogenesis by affecting the serum vasopressin level and SLC12A1 functionality leading to urinary defects in the ADPKD patients [22]. V2R docking-based screening of compounds drug properties reveals that diosmetin, hispidulin and luteolin show better drug properties, whereas luteolin with molecular weight 286 g/mol shows best properties as compared to other compounds. Furthermore, as compared to diosmetin and hispidulin, luteolin forms Pi-Alkali bonding (Cys192, Ala98, Pro95) and conventional H-bonding with Phe105(2.26 Å and 2.96 Å), Gln119(2.78 Å) & Lys116(2.16 Å), the key amino acids having potential role in pathogenesis according to literature reference and predicted active site. Luteolin has anti-inflammatory and anticancer properties linked to the activation of apoptosis, as well as the inhibition of cell proliferation, metastasis, and angiogenesis [23]. Luteolin may restore renal dysfunction, histological damage from renal injury, oxidative stress, neutrophil aggregation, inflammatory reaction, apoptosis, and endoplasmic reticulum stress, according to research on rats [24]. Luteolin derived from *P. Murex* can be used as a possible drug candidate based on the in silico study. In addition, the above-mentioned finding will be confirmed by in vitro studies.

5 Conclusions

Molecular docking-based screening of compounds from *P. Murex* with V2R target reveals that amino acids having potential role in the cystogenesis show interaction with receptor. Three of the compounds, diosmetin, hispidulin, and luteolin, exhibit improved pharmacokinetic and therapeutic characteristics. However, based on the number of parameters and overall drug score, luteolin was found as the best appropriate ligand when compared to others. The best pharmacological features and the most persistent receptor bonding observed in luteolin were reviled by type of bonding interaction. As a result, luteolin-based medicines may be a viable choice for treating ADPKD.

Abbreviations

V2R: Vasopressin 2 receptor; AD: Autosomal dominant; PKD: Polycistic kideney disease; GPCR: G-protein coupled receptor; ADME: Absorption, distribution, metabolism and excretion; PDB: Protein data bank; RMSD: Root mean square distribution; cAMP: Cyclic adenosine monophosphate; TAL: Thick ascending loop of henle; SLC12A1: Solute carrier family 12 member 1.

Acknowledgements

Authors are duly thankful to Maharaja Agrasen University, Solan (H.P) and Lyallpur Khalsa College, Jalandhar, India for providing the laboratory facility in the Department of Biotechnology, School of Basic and Applied Science, MAU, Solan (H.P.) and Bioinformatics Lab, Post Graduate Department of Biotechnology, Lyallpur Khalsa College, Jalandhar, India.

Authors' contributions

GR as a Ph.D. fellow did this complete research work including screening and docking. SKG has supervised this work. AK and GS helped in the manuscript editing. HL given valuable suggestions. All authors read and approved the manuscript.

Funding

The present study was carried out without any financial support from any funding agency.

Availability of data and materials

Data presented in a coherent way in the result section.

Declarations

Ethics approval and consent to participate

No ethical approval required as work is in silico based.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing financial interests.

Author details

[1]Department of Biotechnology, School of Basic and Applied Sciences, Maharaja Agrasen University, Baddi (Solan), Himachal Pradesh, India. [2]Bioinformatics Lab, P.G. Department of Biotechnology, Lyallpur Khalsa College, Jalandhar,

Punjab, India. [3]Centre for Medical Biotechnology, Maharshi Dyanand University, Rohtak, Haryana, India.

Received: 18 May 2021 Accepted: 16 September 2021
Published online: 09 October 2021

References

1. Chapin HC, Caplan MJ (2010) The cell biology of polycystic kidney disease. J Cell Biol 191(4):701–710. https://doi.org/10.1083/jcb.201006173
2. Van Gastel MDA, Torres VE (2017) Polycystic kidney disease and the vasopressin pathway. Ann Nutr Metab 70(1):43–50. https://doi.org/10.1159/000463063
3. Ram G, Vats T, Kumar A, Singh G, Giri SK (2021) Cross talk between renal transporters and polycystin-1 as a potential molecular target involved in autosomal dominant polycystic kidney disease. Iran J Kidney Dis 15(3):177–189
4. Magenheimer BS, St John PL, Isom KS, Abrahamson DR, De Lisle RC, Wallace DP et al (2006) Early embryonic renal tubules of wild-type and polycystic kidney disease kidneys respond to cAMP stimulation with cystic fibrosis transmembrane conductance regulator/Na(+), K(+),2Cl(-) Co-transporter-dependent cystic dilation. J Am Soc Nephrol 12:3424–3437. https://doi.org/10.1681/ASN.2006030295
5. Lakshmipathi J, Gao Y, Hu C, Stuart D, Genzen J, Ramkumar N et al (2020) Nephron-specific disruption of polycystin-1 induces cyclooxygenase-2-mediated blood pressure reduction independent of cystogenesis. J Am Soc Nephrol 31(6):1243–1254. https://doi.org/10.1681/ASN.2019090934
6. Kaleeswaran B, Ramadevi S, Murugesan R, Srigopalram S, Suman T, Balasubramanian T (2019) Evaluation of anti-urolithiatic potential of ethyl acetate extract of *Pedalium murex* L. on struvite crystal (kidney stone). J Tradit Complem Med. 9(1):24–37
7. Rajashekar V, Rao EU, Srinivas P (2012) Biological activities and medicinal properties of Gokhru (*Pedalium murex* L.). Asian Pac J Trop Biomed 2(7):581–585
8. Chaudhary G, Kaushik N (2017) Phytochemical and pharmacological studies in *Pedalium murex* L. Phytochem Rev 16(5):921–934
9. Patel MK, Mandavia DR, Patel TK, Barvaliya MJ, Tripathi CB (2013) Evaluation of anti-inflammatory, analgesic, and antipyretic effects of ethanolic extract of *Pedalium murex* Linn. fruits. Afr J Tradit Complem Altern Med. 10(4):94–100. https://doi.org/10.4314/ajtcam.v10i4.16
10. Arnold K, Bordoli L, Kopp J, Schwede T (2006) The SWISS-MODEL workspace: a web-based environment for protein structure homology modelling. Bioinformatics 22:195–201. https://doi.org/10.1093/bioinformatics/bti770
11. Schülein R, Zühlke K, Oksche A, Hermosilla R, Furkert J, Rosenthal W (2000) The role of conserved extracellular cysteine residues in vasopressin V2 receptor function and properties of two naturally occurring mutant receptors with additional extracellular cysteine residues. FEBS Lett 466:101–106. https://doi.org/10.1016/S0014-5793(99)01764-0
12. Czaplewski C, Kaźmierkiewicz R, Ciarkowski J (1998) Molecular modeling of the human vasopressin V2 receptor/agonist complex. J Comput Aided Mol Des 12:275–287. https://doi.org/10.1023/A:1007969526447
13. Katanguru L (2017) Chemsketch study of phenobarbital: an antiepileptic drug. Int J Comput Theor Chem 5:25
14. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR (2011) Open babel: an open chemical toolbox. J Cheminform 3:33. https://doi.org/10.1186/1758-2946-3-33
15 Dallakyan S, Olson A (2015) Small-molecule library screening by docking with PyRx. Methods Mol Biol (Clifton, NJ) 1263:243–250. https://doi.org/10.1007/978-1-4939-2269-7_19
16. Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:42717. https://doi.org/10.1038/srep42717
17. Mishra S, Singh P (2016) Hybrid molecules: the privileged scaffolds for various pharmaceuticals. Eur J Med Chem 124:500–536
18. Jarrahpour A, Fathi J, Mimouni M, Hadda TB, Sheikh J, Chohan Z et al (2012) Osiris and Molinspiration (POM) together as a successful support in drug design: antibacterial activity and biopharmaceutical characterization of some azo Schiff bases. Med Chem Res 21(8):1984–1990
19. Biovia DS (2017) Discovery studio visualize, San Diego, CA, USA
20. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC et al (2004) UCSF Chimera—a visualization system for exploratory research and analysis. J Comput Chem 25(13):1605–1612. https://doi.org/10.1002/jcc.20084
21 Patel DK, Laloo D, Kumar R, Hemalatha S (2011) *Pedalium murex* Linn.: an overview of its phytopharmacological aspects. Asian Pac J Trop Med 4(9):748–755
22. Rinschen MM, Schermer B, Benzing T (2014) Vasopressin-2 receptor signaling and autosomal dominant polycystic kidney disease: from bench to bedside and back again. J Am Soc Nephrol 25(6):1140–1147
23. Lin Y, Shi R, Wang X, Shen HM (2008) Luteolin, a flavonoid with potential for cancer prevention and therapy. Curr Cancer Drug Targets 8(7):634–646. https://doi.org/10.2174/156800908786241050
24. Hong X, Xiaojing Z, Gang W, Zhengliang Z, Honghong P, Zhong L (2017) Luteolin treatment protects against renal ischemia-reperfusion injury in rats. Mediators Inflamm. https://doi.org/10.1155/2017/9783893

Publisher's Note