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Targeting Vasopressin 2 Receptor (V2R) in Renal Cystogenesis by Exploring the Nephroprotective Potential of "*Terminalia arjuna*"

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Abstract

Objectives: *Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder, leading to the formation of multiple cysts in the kidneys. It is a major cause of end-stage renal disease (ESRD), which often requires dialysis or a kidney transplant for survival. This research focuses on identifying potential bioactive compounds derived from natural sources that show promise for drug development targeting the V2R gene.* ***Methods:*** *The naturally occurred phytochemical compounds in Terminalia arjuna have multiple bioactive properties in the medical field. Drug illness prediction, molecular docking, and absorption, distribution, metabolism, and excretion (ADME) analysis were employed to identify the most suitable ligand candidates for drug development. The V2R protein and its chains were retrieved from the Protein Data Bank (PDB) after undergoing purification. Ligands with poor binding affinity to the target protein were excluded from further analysis. To evaluate drug-likeness, ADMET and Swiss-ADME analyses were performed. Molecular docking simulations were conducted using PyRx. Additionally, the Ramachandran plot was utilized to illustrate the torsion angles Φ and ψ within the protein backbone, offering insights into the structural conformation.* ***Results:*** *The phytocompound found in Terminalia arjuna has a potential binding affinity with V2R found in molecular docking. ADMET profile and docking showed only one compound with the highest binding affinity, that is arjunolic acid, was found to be the best, which can pose the properties of drugs.* ***Conclusion:*** *The bioactive compounds identified in this study could be regarded as potential drug candidates for inhibiting renal cytogenesis, owing to their promising binding affinity with both structural and non-structural proteins of the virus. These findings suggest that these compounds may play a crucial role in therapeutic strategies aimed at targeting renal disease progression.*

Keywords: Hereditary kidney disease, bioactive compounds, renal cytogenesis inhibition, potential binding affinity, ADMET

INTRODUCTION

A renal cyst is the most common lesion of the kidney. Renal cysts are so ubiquitous that they are present in approximately 40% of patients undergoing imaging. Renal cysts can range from benign to malignant or indeterminate [1]. There are several factors contributing to the formation of renal cysts. The most commonly recognized causes include congenital malformations, gene mutations, various infections, and toxic damage [2, 3]. Polycystic kidney disease (PKD) comes in two genetic forms: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD), each with distinct genetic and clinical characteristics. ADPKD, in particular, is a multisystem disorder

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that involves the development of numerous cysts in the kidneys, leading to an increase in kidney size and ultimately progressing to end-stage kidney disease (ESKD) in most affected individuals [4].

Mutations in the polycystin proteins, specifically polycystin-1 (PC1) and polycystin-2 (PC2), are responsible for the development of autosomal dominant polycystic kidney disease (ADPKD). These mutations lead to the formation of fluid-filled renal cysts that disrupt the normal renal structure and function, eventually resulting in kidney failure for most patients. ADPKD triggers several abnormal signaling pathways, contributing to renal cytogenesis. The genes responsible for encoding PC1 and PC2 are polycystic kidney disease-1 (PKD1) and polycystic kidney disease-2 (PKD2), respectively. Under normal conditions, these proteins form a complex vital for maintaining renal architecture. However, this functionality is compromised when the Gα-subunit of a G-protein-coupled receptor (GPCR) binds to PC1, activating a series of aberrant signaling pathways that promote disease progression. The sodium/potassium/chloride co-transporter, encoded by the SLC12A1 gene (responsible for NKCC2), is essential for renal function. This co-transporter is localized in the apical membrane of the thick ascending loop of Henle (TAL) and is regulated by the vasopressin 2 receptor (V2R) protein. The interaction between SLC12A1 and other renal transporter proteins is crucial for maintaining proper ion transport and normal kidney function. In ADPKD, elevated vasopressin levels lead to increased intracellular cyclic AMP (cAMP), causing an imbalance in the SLC12A1 co-transporter. This results in decreased calcium levels and impaired chloride secretion from the cyst-lining cells. The vasopressin 2 receptor becomes dysfunctional, with elevated cAMP levels playing a central role in the progression of ADPKD. This disruption of ion balance contributes to the formation and enlargement of cysts, exacerbating kidney dysfunction [5–7].

Vasopressin, also known as antidiuretic hormone (ADH) or arginine vasopressin (AVP), is the primary hormone responsible for regulating water balance in the body through its antidiuretic effects in the kidneys. It is synthesized in the hypothalamus and released into the bloodstream by the posterior pituitary gland. Hypothalamic osmotic neurons play a key role in triggering the release of AVP. Once released, AVP binds to V2 receptors in the kidneys, which activates a signaling cascade involving the production of cyclic AMP (cAMP). This leads to the phosphorylation of Aquaporin 2 (AQP2) water channels in the collecting ducts of the kidneys, facilitating water reabsorption and maintaining fluid balance in the body [8]. In the human kidney, the vasopressin 2 receptor (V2R) is primarily expressed in the collecting ducts and the medullary thick ascending limb of the loop of Henle. Activation of V2R by its ligands leads to increased intracellular cyclic AMP (cAMP) levels, triggering a series of downstream signaling events. These include the activation of cAMP effectors such as protein kinase A (PKA), exchange protein directly activated by cAMP (Epac), and phosphorylated extracellular signal-regulated kinase (ERK). These effectors phosphorylate several intracellular targets, including the Aquaporin 2 (AQP2) water channels and the cAMP response element-binding protein (CREB), a transcription factor.

Together, these molecular events promote cell proliferation and fluid secretion, two key mechanisms that drive the progression of cyst formation and growth in polycystic kidney disease (PKD). As a result, blocking the V2R pathway has emerged as a promising therapeutic strategy for slowing down cystogenesis and treating PKD [9].

In ancient times, herbal medicines served as a primary source of therapeutic agents for treating various ailments. "*Terminalia arjuna*" (TA) is one of the most frequently used medicinal trees in India traditional medicinal system [10]. *Terminalia arjuna* is an evergreen tree from the *Combretaceae* family, widely recognized for its traditional medicinal applications. While all parts of the plant possess medicinal properties due to specific bioactive compounds, the bark is particularly noted for treating various ailments, including cardiovascular issues, skin conditions, asthma, hypertension, urinary tract disorders, liver cysts, and renal cysts, as utilized by traditional ethnic healers. Key bioactive constituents of *Terminalia arjuna* include glycosides (cardiac glucosides), flavonoids (such as arjunone and arjunolone), and triterpenoids (like arjunolic acid). These compounds contribute to the plant's

cardioprotective, antioxidant, wound healing (with tannins and saponins found in the bark), anti-tumor (notably against human hepatoma), anti-inflammatory, anti-diabetic, and broad-spectrum antimicrobial activities, particularly against various gram-negative bacteria [11].

The present studies suggest that arjunolic acid have significant binding affinity. The therapeutic strategies against the vasopressin 2 receptor interpreted based on molecular binding and interactions suggest that the potential drug can be used for further research work.

MATERIALS AND METHODS

Selection of the Target Protein

The three-dimensional structure of the target vasopressin 2 receptor (7DF9) protein was downloaded in PDB format from the RCSB Protein Data Bank (https://www.rcsb.org/). The protein was visualized using Discovery Studio 2021 v21.1.0.20298 from BIOVIA (available at https://discover.3ds.com). During this process, water molecules, ions, and ligands were removed to create a clearer representation of the protein structure. The modified protein was then saved in PDB format to facilitate further analysis.

STRUCTURE VALIDATION

Ramachandran Plot

The Ramachandran plot visualized the amino acids in the energetically allowed regions based on the torsion angle ψ and Φ, which refers to the rotation of the polypeptide chain around the two bonds on the sides of the Cα atom. The Ramachandran plot of 7FD9 protein was obtained using the Pictorial database of 3D structure (PDBsum) (https://www.ebi.uc.uk/thornton-srv/database/pdbsum/) and PROCHECK (https://www.ebi.uc.uk/thornton-srv/software/PROCHECK).

Secondary Structure

The secondary structure of the protein was analyzed in the PDB sum. Which shows it has 360 residues.

Selection of the Ligand

The phytochemical compound was extracted and later considered for the molecular docking study. The phytochemicals selected from the Indian medicinal plants, phytochemistry, and therapeutics (IMPPAT) database (*https://cb.imsc.res.in/imppat/*) have been listed as the medical plants and 3D structure downloaded in the structure-data file (SDF) format from PubChem (*https://pubchem.ncbi.nlm.nih.gov/*). Canonical SMILES data of phytocompounds was collected for further analysis.

In Silico ADME Analysis

Physicochemical properties, pharmacokinetics and druglikeliness are used by evaluating the ligand using Swiss-ADME analysis (*https://www.swissadme.eh/index.php*). The conical SMILES of ligands were obtained in the PubChem database.

Molecular Docking

V2R protein target-based screening compounds were tested with purified macromolecules to find leads of compounds. The virtual molecular screening was carried out using the AutoDock Vina with the help of the PyRx virtual screening tool version Python prescription 0.8 (*https://sourceforge.net/projects/pyrx/*). Phytochemicals were converted into a pbdqt file format before using the virtual screening docking. The docking results obtained in binding energy (Kcal/mol) of phytochemicals interactions with the protein were converted in a CVS file format. The affinity binding score was more negative and chosen for further analysis. The ligand out in pdbqt file was downloaded in PDB file format from PyRx and was submitted to the BIOVIA-Discovery Studio Visualizer to observe the structure and interaction between ligands and target protein.

RESULTS

Selection of Target Protein

The V2R gene was screened with the help of KGGE and was selected as a protein target. The crystal structure of the vasopressin 2 receptor (V2R) domain with PDB ID: 7DF9 protein model was selected and downloaded in PDB file format. Purification of protein is done by the BIOVIA tool, where ligand and water molecules were removed as shown in Figure 1.

Protein Structure Analysis

Ramachandran Plot

The plot statistics observed non-glycerin and non-proline 687 residues from a total of 800 residues. The plot shows red color for the most favored regions represented by A, B, and L with 529 residues; additional allowed regions represented by a, b, l, and p indicating brown color with 155 residues; generously allowed regions represented by ~a, ~b, ~L, ~p in yellow with 3 residues; disallowed region represented by XX indicates faint yellow color with 0 residues. The analysis excluded the end residues, specifically glycine and proline, totaling 12 amino acid residues. Glycine (Gly) and proline (Pro) residues at positions 49 and 52, respectively, were further evaluated in the statistical plots presented in Figure 2. This assessment was based on an analysis of 118 protein structures with a resolution of at least 2.0 Å and an R-factor no greater than 20.0. A high-quality model is expected to show over 90% of its residues in the most favored regions (A, B, and L) of the Ramachandran plot.

Secondary Structure

The structure has a total of 360 residues. The 7FD9 protein secondary structure has 4 sheets. 7 beta hairpins, 5 beta bulges, 21 strands, 4 helices, 26 beta turns, and 7 gamma turns, as shown in Figure 3.

Retrieval of Phytocompounds

Twenty-five phytocompounds of *Terminalia arjuna* were selected for screening from IMPPAT, and their 3D structures were obtained from PubChem, as shown Table 1.

ADME Analysis

The screening of ADME properties was obtained by using Swiss-ADME, as shown in Tables 2–4.

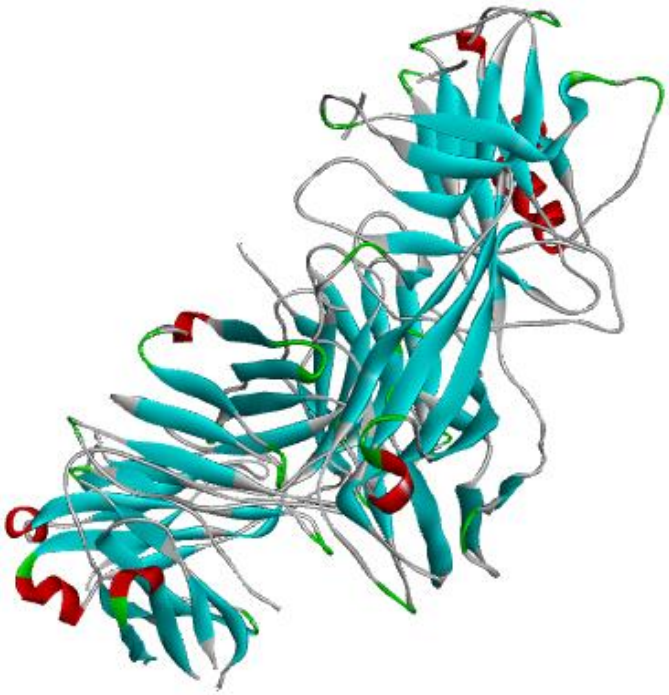

Figure 1. Crystal of arrestin2-V2Rpp-1-Fab30 complex.

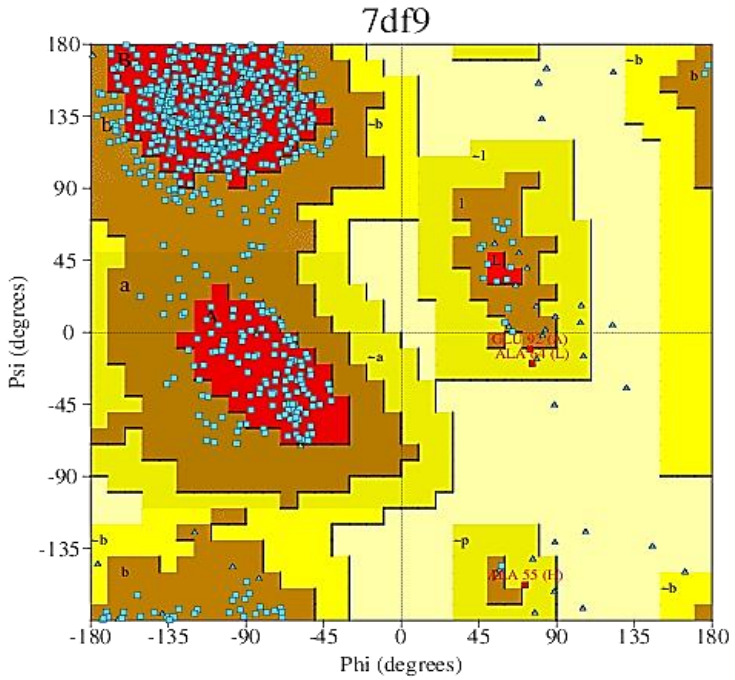

Figure 2. Ramachandran plot.

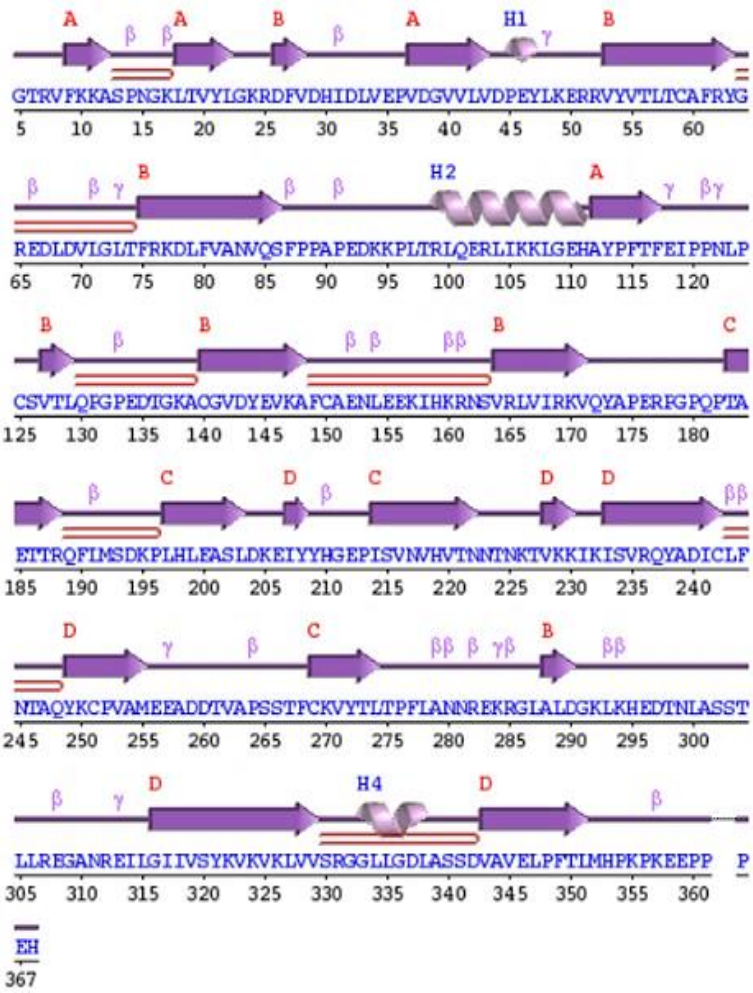

Figure 3. Secondary structure of V2R protein.

Table 1. Phytocompounds obtained from IMPPAT database.

Phytochemical name	PUBChem ID
Arjunic acid	15385516
Catechol	289
Ellagic acid	5281855
Oxalic acid	971
Arjunolic acid	73641
Mannitol	6251
Epigallocatechin	72277
Oleanolic acid	10494
Leucodelphidin	440835
Tomentosic acid	622032
Arjungenin	1244386
Cerasisin	14034812
Myristyl oleate	5365034
Hentriacontane	12410
Arachidic acid	10467
Methyl oleanolate	92900
Friedelin	91472
Gallic acid	370
8-Hydroxyhexadecanoic acid	15569773
Arjunglucoside I	14658050
Beta-sitosterol	222284
Baicalein	5281605
Catechol	289
Stearate	3033836
(+)-Gallocatechin	65084

Physicochemical Properties

Physicochemical properties are also referred to as physical properties, solvation properties, or molecular properties (e.g., molecular weight, dipole moment, polarizability, etc.) related to interactions with different media and properties or media attributes that define intrinsic chemical reactivity. The size (molecular weight), H-acceptors, H-donars, and A tropical polar surface area (TPSA) were checked in as shown in Table 2.

Pharmacokinetics

Pharmacokinetics (PK) is the study of how the body interacts with administered substances throughout the entire duration of exposure. This field focuses on understanding the absorption, distribution, metabolism, and excretion of various substances, which may include chemical xenobiotics such as pharmaceutical drugs, pesticides, food additives, and cosmetics. By examining these processes, pharmacokinetics provides valuable insights into the behavior of these substances within the body, informing safety, efficacy, and dosage considerations in various applications. The BBB, GI absorption, and PGB substrate are the major properties. The BBB restricts compound permeation into the brain, whereas GI absorption improves the efficacy of the drug, as shown in Table 3.

Drug-likeness

Drug-likeness refers to the similarity of the products between compounds and existing drugs with respect to factors like bioavailability. Drugs like compounds are more likely to be transformed into drugs. The Lipinski parameters with 0 violations and the bioavailability score are the properties checked, as shown in Table 4.

Table 2. Physiochemical properties.

Ligand	Formula	MW	H-acceptors	H-donars	TPSA
Arjunic acid	$C_{30}H_{48}O_5$	488.7	5	4	97.99
Catechol	$C_6H_6O_2$	110.11	2	2	40.46
Ellagic acid	$C_{14}H_6O_8$	302.19	8	4	141.34
Oxalic acid	$C_2H_2O_4$	90.03	4	2	74.6
Arjunolic acid	$C_{30}H_{48}O_5$	488.7	5	4	97.99
Mannitol	$C_6H_{14}O_6$	182.17	6	6	121.38
Epigallacatechin	$C_{15}H_{14}O_7$	306.27	7	6	130.61
Oleanolic acid	$C_{30}H_{48}O_3$	456.7	3	2	57.53
Leucodelphidin	$C_{13}H_{14}O_8$	322.27	8	7	150.84
Tomentosic acid	$C_{30}H_{48}O_6$	504.7	6	5	118.22
Arjungenin	$C_{30}H_{48}O_6$	504.7	6	5	118.22
Cerasidin	$C_{19}H_{20}O_6$	344.36	6	1	74.22
Myristyl oleate	$C_{32}H_{62}O_2$	478.83	2	0	26.3
Hentriacontane	$C_{31}H_{64}$	436.84	0	0	0
Arachidic acid	$C_{20}H_{40}O_2$	312.53	2	1	37.3
Methyl oleanolate	$C_{31}H_{50}O_3$	470.73	3	1	46.53
Friedelin	$C_{30}H_{50}O$	426.72	1	0	17.07
Gallic acid	$C_7H_6O_5$	170.12	5	4	97.99
8Hydroxyhexadecanoic acid	-	0	5	4	0
Arjunlucoside I	$C_{36}H_{58}O_{11}$	666.84	11	8	197.37
Beta-Sitosterol	$C_{29}H_{50}O$	414.71	1	1	20.23
Baicalein	$C_{15}H_{10}O_5$	270.24	5	3	90.9
Catechol	$C_6H_6O_2$	110.11	2	2	40.46
Stearate	$C_{18}H_{35}O_2$		2	0	40.13
(+)-Gallocatechin	$C_{15}H_{14}O_7$		7	6	130.61

Table 3. Pharmacokinetics.

Ligand	GI	BBB	P-gp substrate
Arjunic acid	High	No	Yes
Catechol	High	Yes	No
Ellagic acid	High	No	No
Oxalic acid	High	No	No
Arjunolic acid	High	No	Yes
Mannitol	Low	No	No
Epigallocatechin	High	No	No
Oleanolic acid	Low	No	No
Leucodelphidin	Low	No	No
Tomentosic	High	No	Yes
Arjungenin	High	No	Yes
Cerasidin	High	Yes	No
Myristyl oleate	Low	No	Yes
Hentriacontane	Low	No	Yes
Arachidic acid	Low	No	No
Methyl oleanolate	Low	No	No
Friedelin	Low	No	No
Gallic acid	High	No	No
8-Hydroxyhexadecanoic acid	High	No	No

Arjunlucoside 1	Low	No	Yes
Beta-Sitosterol	Low	No	No
Baicalein	High	No	No
Catechol	High	Yes	No
Stearate	High	Yes	No
(+)-Gallocatechin	High	No	No

Table 4. Drug-likeness.

Ligand	Lipinski violation	Bioavailability score
Arjunic acid	0	0.56
Catechol	0	0.55
Ellagic acid	0	0.55
Oxalic acid	0	0.85
Arjunolic acid	0	0.56
Mannitol	1	0.55
Epigallacatechin	1	0.55
Oleanolic acid	1	0.85
Leucodelphidin	1	0.55
Tomentosic	1	0.56
Arjungenin	1	0.56
Cerasidin	0	0.55
Myristyl oleate	1	0.55
Hentriacontane	1	0.55
Arachidic acid	1	0.85
Methyl oleanolate	1	0.55
Friedelin	1	0.55
Gallic acid	0	0.56
8-hydroxyhexadecanoic acid	0	0.56
Arjunlucoside I	3	0.17
Beta-sitosterol	1	0.55
Baicalein	0	0.55
Catechol	0	0.55
Stearate	1	0.85
(+)-Gallocatechin	1	0.55

After the ADME analysis out of all 25 ligands obtained, only 10 ligands with GI-High, 0 Lipinski violation were selected for molecular docking.

Molecular Docking

As per Table 5 screened. Ten ligands were obtained from twenty-five phytocompounds of *Terminalia arjuna.* The obtained ten ligands were used again for molecular docking, and the best one ligand that is arjunolic acid has got the greater binding affinity that is -9.3 to the target and use for further analysis. The PyRx tool was used for molecular AutoDock.

After molecular docking in PyRx, visualization of ligand interaction is done in Discovery Studio 2021 v21.1.0.20298 (BIOVIA). The 2D ligand interactions were illustrated in relation to the amino acids of the macromolecule, highlighting various types of interactions such as van der Waals forces, conventional hydrogen bonds, carbon-hydrogen bonds, pi-donor hydrogen bonds, pi-sigma interactions, pi-pi stacking, pi-alkyl interactions, alkyl interactions, and unfavorable donor-donor interactions, each represented by specific colors for clarity.

Table 5. Binding affinity of ligands from PyRx.

Ligand	Binding affinity
Cerasidin	--8.2
Arjunic acid	-9.2
8-Hydroxyhexadecanoic acid	-6.1
Catechol	-5.1
Gallic acid	-6.5
Baicalein	-9.1
Ellagic acid	-8.1
Arjunolic acid	-9.3
Oxalic acid	-4.1
Catechol	-5.1

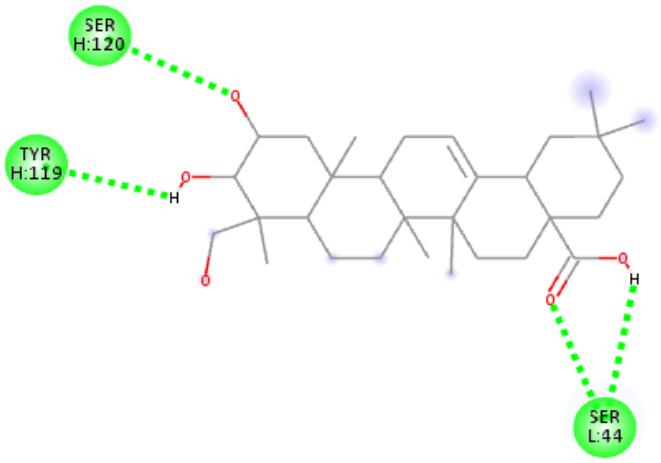

Figure 4. 2D visualization of arjunolic acid.

This detailed depiction aids in understanding the nature and strength of the binding interactions between the ligand and the target macromolecule. Docking interactions of arjunolic acid were interpreted from the 2D analysis, as shown in Figure 4. The green color chain shows the interaction of the conventional hydrogen bond.

DISCUSSION

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent monogenic cause of end-stage kidney disease (ESKD). Genetic studies involving patients and animal models have significantly contributed to our understanding of the disease's pathobiology, strongly supporting a "threshold model." According to this model, cyst formation is initiated when the functional dosage of polycystins drops below a critical threshold within individual tubular epithelial cells. This reduction can result from several factors, including: (a) germline and somatic mutations in the PKD1 or PKD2 genes; (b) mutations in genes associated with the endoplasmic reticulum protein biosynthetic pathway (such as SEC63, SEC61B, GANAB, PRKCSH, DNAJB11, ALG8, and ALG9); and (c) somatic mosaicism. In ADPKD, the progression of fibrosis plays a significant role in renal failure, ultimately leading to ESKD. The vasopressin type-2 receptor (V2R) is instrumental in regulating renal water homeostasis and stimulates cyst expansion in the context of ADPKD. In both humans and rodents, arginine vasopressin (AVP) influences a variety of physiological functions, including fluid balance, blood osmolarity, reproductive processes, complex behaviors, and cognitive functions such as memory and learning [12, 13]. The renal system consists of approx. one million nephrons in the kidney and have a glomerular filtration rate of 120 ml/min. The renal system major function is to maintain homeostasis at the acid-base level, electrolyte maintenance and detoxification of endogenesis waste compounds and exogenous toxic compounds. The exogenous compounds or toxicants enter the renal system via blood

plasma through gastrointestinal system or the lungs, which can be excreted out through the glomerular filtration and distal tubules through passive and active transport [14, 15]. *Terminalia arjuna* has demonstrated effectiveness as an antioxidant, providing protection against cardiovascular diseases and playing a significant role in regulating the body's hormonal system. It has also been beneficial in treating various skin conditions, including eczema, itching, rashes, scars, and more severe issues such as psoriasis, with regular use.

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by localized autonomous cellular proliferation, fluid accumulation within renal cysts, and intra-parenchymal fibrosis of the kidneys. Common complications associated with ADPKD include hypertension, gross hematuria, cyst rupture and infection, kidney stones, and flank pain. Additionally, patients may experience extra-renal manifestations, such as liver and pancreatic cysts, vascular aneurysms, cardiac valve abnormalities, hernias, and diverticulosis [16].

CONCLUSION

According to the analysis, results, and study, *Terminalia arjuna* has arjunolic acid, which has anti-inflammatory, anti-diabetic, antimicrobial, and antioxidant activity. In docking, arjunolic acid has an affective binding affinity with V2R protein and is fit for potential drug candidates.

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Abbreviation

ARPKD: Autosomal Recessive Polycystic Kidney Disease
ADH: Antidiuretic Hormone
AVP: Arginine Vasopressin
BBB: Blood-Brain Barrier
ESKD: End-Stage Kidney Disease
GI: Gastrointestinal
IMPPAT: Indian Medical Plants, Phytochemistry and Therapeutics
MW: Molecular Weight
PC-1 & PC-2: Polycystin-1 & Polycystin-2
PKD-1 & PKD-2: Polycystic Kidney Disease-1 & Polycystic Kidney Disease-2
PK: Pharmacokinetics
TA: Terminalia Arjuna
TPSA: Topological Polar Surface Area
V2R: Vasopressin 2 Receptor

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