Original Article

Thai Journal of Pharmaceutical Sciences

In silico screening of natural compounds to identify lead as interleukin 17A receptor blockers as antihypertensive agents

Jimish R. Patel[1,2], Hirak V. Joshi[3], Ujashkumar A. Shah[3], Jayvadan K. Patel[3]

[1]Department of Pharmaceutical Chemistry, Shri B M Shah College of Pharmaceutical Education and Research, Modasa, Gujarat, India, [2]Department of Pharmaceutical Chemistry, Sankalchand Patel University, Visnagar, Gujarat, India, [3]Department of Quality Assurance and Pharmaceutical Chemistry, Nootan Pharmacy College, Sankalchand Patel University, Visnagar, Gujarat, India

Corresponding Author: Jimish R. Patel, Department of Pharmaceutical Chemistry, Shri B M Shah College of Pharmaceutical Education and Research, Modasa, Gujarat, India. Phone: +91- 9429633525. Fax: +91-2774-249482. E-mail: jimish_patel_1986@yahoo.co.in

Received: Jun 04, 2020
Accepted: Jul 16, 2020
Published: Jul 16, 2020

ABSTRACT

Objectives: Nature gives disease and nature gives the medicine. Natural products have exhibited paramount sources of novel drugs. Due to this, natural products have gained a dominant role in drug design and discovery. Interleukin 17 (IL-17) is a potent pro-inflammatory cytokine produced by activated memory T cells. Recent studies have created a vast amount of interest in the IL-17A as it is a key novel marker for the new potential therapeutic target for antihypertensive treatment. **Materials and Methods:** The X-ray crystallographic proteins of novel antihypertensive target IL-17A receptor blocker PDB ID 5hi3 were selected as receptors. The research has been carried out using computer-aided drug design to identify natural compounds using virtual screening to establish as a novel lead compound for a novel target of antihypertensive by inhibition IL-17A receptor blocker. **Results:** Out of 151 natural compounds, our research finding has put natural compound gamma (γ)-oryzanol which is a lead compound for developing novel IL-17A receptor blocker as antihypertensive agents. **Conclusions:** Therefore, the findings of this study may help researchers to identify new molecules or design of new molecules which can specifically be used as novel target IL-17A receptor blocker as antihypertensive agents after lead optimization.

Keywords: Antihypertensive, gamma (γ)-oryzanol, interleukin 17A blockers, virtual screening

INTRODUCTION

Cardiac disease and heart stroke data from the American Heart Association show that in recent total death, 17 million and every year.[1] Blood pressure (BP) control is the main challenge for the health-care system. As it is evident that many antihypertensive classes are currently available in market but these drugs have many serious side effects, drug-drug contraindication and having low potency. Therefore, there is an urgent need to develop newer antihypertensive drugs with improved potency along with fewer side effects.[2] Many natural plants have been used as hypotensive effects.[3] According to The World Health Organization, world's 80% of people primarily use traditional medicine of plant origin.[4] Approximately 25% of synthetic allopathic medicine lead analogs derived on plants base. However, herbal Ayurvedic medicine used to develop novel drug design to potent and effective lead molecules for antihypertensive treatments.[5] The term interleukin derives from two words such as "*inter*" and "*leukin*," "*inter*" means of contact, and "*leukin*" means leukocytes. The function of the immune system depends on a large part on interleukins is a group of cytokines they secreted proteins and signaling molecules. Interleukin 17 (IL-17) is a potent pro-inflammatory cytokine produced by activated memory T cells. The role of inflammatory mediators such as T cells and cytokines is well established in the treatment of hypertension.[6,7] The IL-17A was thought to represent a distinct signaling system that appears to have been highly conserved across vertebrate evolution.[8] The IL-17A is a key novel marker for the new potential therapeutic target for antihypertensive treatment [Figure 1].[9,10]

An essential component is inflammation in pathophysiology for arterial hypertension activity. Arterial hypertension is not

the only formation of hypertension but also organ damage, endothelial infection, complex immune reaction, cell metabolic, or chemical disturbance leading to phenotype.[11] Angiotensin-II is an effect on the immune system without the absence of arterial hypertensive activity. Angiotensin-II is not the only effect on arterial hypertension but also affects tissue necrosis factor-alpha producing angiotensin-converting enzyme and organ damage.[12,13]

Medicinal chemists today are facing a significant challenge because of the increased cost and long time taken to discover a new drug, and also because of severe competition amongst different drug companies. Computer-aided drug design (Docking) can also help in the understanding of different ligand-protein complexes for novel drug design and discovery process. The present work aims to design and discover novel natural molecules as lead compounds as interleukin-17A inhibitors as antihypertensive compounds.

MATERIALS AND METHODS

Materials

The X-ray crystallographic protein-ligands IL-17A antagonists PDB ID 5hi3 structure was downloaded from the protein databank.[14] In this research work, various active constitutes of plants have been identified from various well-established literature database.[3] Chemical structures were downloaded from a different database such as PubChem, ChemSpider, and CHEBI. Discovery studio 3.5 was used for Protein structure, MGL tools were used to generate protein and ligand PDBQT file, ChemDraw was used for geometrics and optimization of the 3D structure, and AutoDock Vina was used for docking study.

Methodology

Protein structure preparation

In this study, from protein databank, the X-ray crystal protein PDB 5HI3 was downloaded and used in this study [Figure 2]. The PDB was prepared in Discovery studio and this PDB file was converted to PDBQT in AutoDock.[14-16]

Ligand structure preparation

A total of 150 active constitutes derived from plants have been utilized in this study which was aimed at targeting IL-17A antagonists for antihypertensive activity. The chemical constituent's structures converted 2D to 3D and analysis using ChemBioOffice.[17]

Docking Process using by AutoDock Vina

The docking is performed by AutoDock Vina developed by Scripps Research Institute.[18] Polar hydrogens were added to PDB and torsional bonds were also added to a ligand by ligand module. IL-17A receptor inhibitor protein was added polar hydrogens, torsional bonds of ligands were set free by ligand module, and grid box size was selected 40x40x40 along the X, Y, and Z axes with 0.375 Å spacing. The grid center was set to 78.451, –41.659, and –48.832 along the X, Y, and Z axes using MGL tools 1.5.6. Docking score was calculated using AutoDock. All visualization and graphic representations were performed by the Discovery studio 3.5 Molecular Graphics Visualize software.

ADMET Prediction

Our research finding identifies gamma (γ)-oryzanol as a lead compound for developing novel IL-17A receptor blocker. ADMET (absorption, distribution, metabolism, excretion, and toxicity) studies are carried out by software programs.[19,20] The pharmacokinetic (ADMET) profile of a drug molecule is very essential in estimating its pharmacodynamic activities.

RESULTS AND DISCUSSION

The various plant chemical constituents were docked in IL-17A receptor active site. The comparative binding energy of IL-17A receptor blockers with their respective natural substrate and PDB ID: 5HI3 is shown in Table 1. The detail of binding affinity is shown for the active site of IL-17A receptor.

Out of 151 natural compounds, our research finding has put natural compound gamma (γ)-oryzanol as a lead compound for developing novel IL-17A receptor blocker as antihypertensive agents. The reason behind this is the binding energy of gamma (γ)-oryzanol is as –11.3 kcal/mol

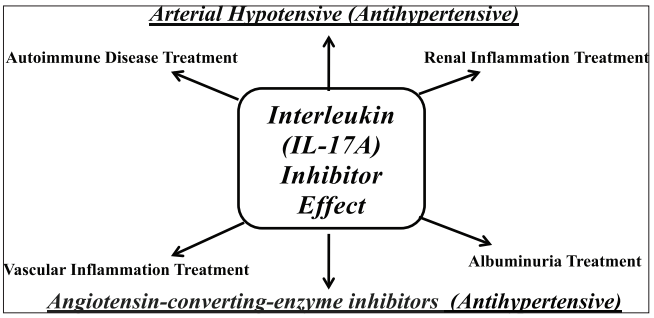

Figure 1: Implication of interleukin 17A in antihypertensive treatment

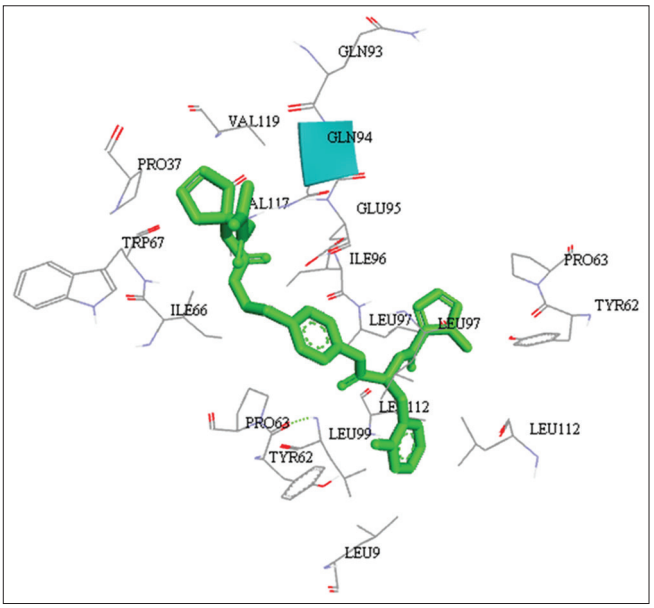

Figure 2: Structure of protein PDB 5HI3 ligand interacting drug interleukin 17A inhibitor

Table 1: Comparative binding energy of interleukin 17A receptor blockers with their respective natural substrate and PDB ID: 5HI3

Naturally drug names	Chemical constituents	Potent affinity (interleukins) (kcal/mol)	Comparison with PDB ID: 5HI3 Docking Score
American hellebore	Jervine	–10.6	Interleukin-17A Inhibition PDB ID: 5HI3 drug AutoDock Vina score –9.3 kcal/mol
Ashwagandha	Withanolides	–10.4	
Asian rice	γ-Oryzanol	–11.3	
Asparagus	Sarsasapogenin	–10.3	
Banana	Naringin	–9.7	
Barberry	Berbamine	–10.2	
Black currant leaf	(–)-epicatechin gallate	–10.3	
Black mulberry	Cyclomorusin	–10.3	
Black nightshade	Tigogenin	–10.9	
Calendula, (marigold)	Faradiol	–9.9	
Castor	Kaempferol-3O-D-rutinoside	–9.8	
	Rutin	–9.8	
Chinese peony	1,2,3,4,6-pentagalloyl-beta-D-glucopyranoside	–10.1	
Conessi, (kurchi)	Regholarrhenine-B	–9.3	
Corn cockle	Aglycone githagenin (Gypsogenin)	–9.8	
Corydalis	Tetrahydrocoptisine	–9.3	
East Indian Rosebay	α-amyrin acetate	–11.1	
American mistletoe, eastern mistletoe, hairy mistletoe and oak mistletoe	Morolic acid	–9.4	
Eclipta	β-amyrin	–9.3	
Fang ji, Han fang ji	Stepholidine	–10.5	
Goldenseal	Coptisine	–9.3	
Horny Goat Weed, Barrenwort, Yinyanghuo, bishop's hat, fairy wings, yin yang huo	Icariin	–9.3	
Indian Barberry, Tree Turmeric	Berbamine	–10.2	
Napellus	Quercetin 3-O-a-L-rhamno pyranosyl -(1→6)-b-Dgalactopyranoside-7-O-a-L-rhamnopyranoside	–10.5	
Jatamansi, Indian Nard	Lupeol	–9.9	
Jiaogulan	Gynostemma pentaphyllum (Bacoside A)	–9.9	
Mistletoe	Beta-amyrin	–9.3	
Olive	*β*-amyrin	–9.3	
Oriental Bittersweet	3-oxoolean-12-en-28-oic acid, hedragonic acid	–9.7	
Rehmannia, Chinese Foxglove	Isoacteoside	–9.9	
Squill, Sea Onion	Bufadienolides	–10.1	
Strophanthus, Climbing Oleander	Strogoside	–10.2	

[Figure 3], which is good with the comparison of drug bacoside A [Table 2].

Having good inhibition at the binding site for activity, the interaction with amino acids such as ASP42, LEU-99, PRO37, SER31, SER41, TYR43, TYR44, TYR-62, GLU95, and LYS114 is essential. Furthermore, LEU-97, LEU-99, SER-41, TYR-43, TYR-62, GLU95, and LYS114 were known to form a strong hydrogen bond with oxygen, carbon, and nitrogen atoms of either amino acid. This has been clearly seen with gamma (γ)-oryzanol.

Ordinary amino acid such as LEU-99, SER-41, TYR-43, TYR-62, GLU95, and LYS114 plays a key role in the selectivity and binding affinity of inhibitors. Therefore, we can hypothesize that the antihypertensive quality of PDB ID: 5HI3 ligand is due to its action in inhibiting the interleukin-17A inhibition. The results of docking analysis showed that known interleukin-17A

Table 2: Stereo view of PDB ID 5HI3 interacting with most active natural chemical constituent gamma (γ)-oryzanol

PDB ID	Most active chemical constituent evaluation	Amino acid With position		No. of hydrogen bond formed	Interleukin-17A inhibition score (kcal/mol)
		Protein chain	Amino acid		
PDB id: 5HI3	Gamma (γ)-oryzanol	A	ASP42	10	–11.3
			LEU-99		
			PRO37		
			SER31		
			SER41		
			TYR43		
			TYR44		
			TYR-62		
		B	GLU95		
			LYS114		
PDB id: 5HI3	InChIKey (VWRXSIAIHJZTCV-MHZLTWQESA-N) PDB ID: 5HI3 inhibitor synthetic ligand from PDB ID: 5HI3	A	LEU-97	7	–9.3
			LEU-99		
			SER-41		
			TYR-43		
			TYR-62		
		B	GLU95		
			LYS114		

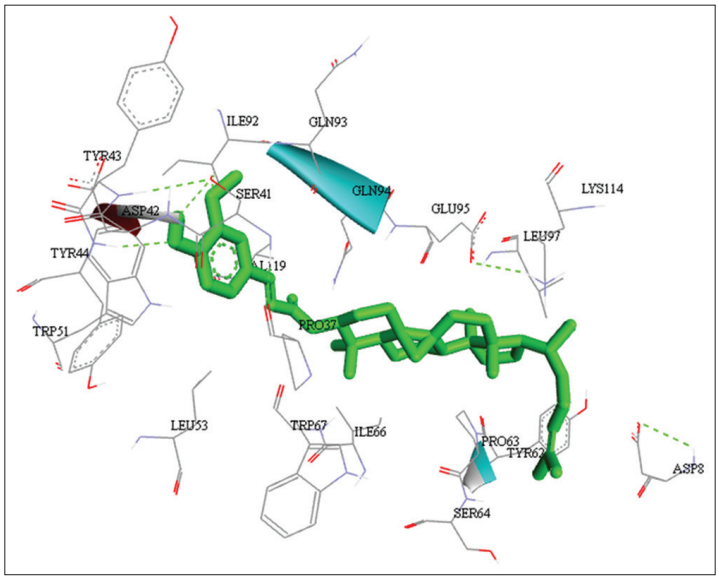

Figure 3: Binding interaction of gamma (γ)-oryzanol in active site of interleukin 17A receptor

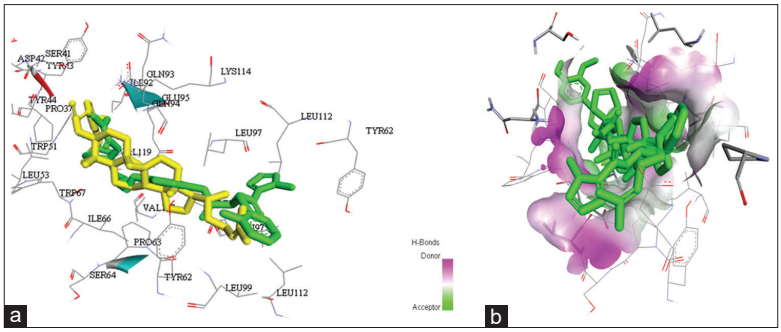

Figure 4: (a) Superimposition of PDB ID: 5HI3 ligand and gamma (γ)-oryzanol in binding pocket of interleukin-17A receptor active site (b) hydrogen bond donor and acceptor pose

Table 3: ADMET predicted parameters of gamma (γ)-oryzanol

ADMET parameters	Property with unit	Predicted value
Absorption	Water solubility (log mol/L)	–4.238
	Caco2 permeability (log Papp in 10^{-6} cm/s)	1.552
	Intestinal absorption (human) (% Absorbed)	97.019
	Skin permeability (log Kp)	–2.734
	P-glycoprotein substrate	Yes
	P-glycoprotein I inhibitor	Yes
	P-glycoprotein II inhibitor	Yes
Distribution	VDss (human) (log L/kg)	–0.69
	Fraction unbound (human) (Fu)	0.045
	BBB permeability(log BB)	–0.709
	CNS permeability (log PS)	–0.973
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	Yes
	CYP1A2 inhibitor	No
	CYP2C19 inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	Yes
Excretion	Total Clearance (log ml/min/kg)	–0.182
	Renal OCT2 substrate	No
Toxicity	AMES toxicity	No
	Max. tolerated dose (human) (log mg/kg/day)	0.548
	hERG I inhibitor	No
	hERG II inhibitor	No
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.614
	Oral rat chronic toxicity (LOAEL) (log mg/kg_bw/day)	2.357
	Hepatotoxicity	No
	Skin sensitization	No
	T. pyriformis toxicity (log ug/L)	0.285
	Minnow toxicity (log mM)	–5.136

inhibition (5HI3 ligand) shares a common binding site of gamma (γ)-oryzanol [Figure 4]. The docking results were validated by RMSD (root mean square deviation) value (0.375 Å) and protein structure validated by Ramachandran plot. ADMET studies for active chemical constituent gamma (γ)-oryzanol are carried out by software programs [Table 3].

CONCLUSIONS

In this *in silico* screening, out of 151 natural compounds, the gamma (γ)-oryzanol has a good affinity (Docking score –11.3 kcal/mol) compared to PDB ID: 5HI3 ligand. Therefore, our computational study can serve gamma (γ)-oryzanol as a "lead compound" for further exploring more potent compounds as interleukin-17A inhibitors. Therefore, the findings of this study may help researchers to identify new molecules or design of new molecules which can specifically be used as novel target IL-17A receptor blocker as antihypertensive agents after lead optimization. These findings have given structural insights into binding requirements which is useful to design active therapeutic compounds. The research finding has identified possible interleukin-17A inhibitors. In the future, by doing optimization of lead compounds, more potent compounds can be discovered for the interleukin-17A inhibition and can give an excellent breakthrough novel target in antihypertensive drugs.

ACKNOWLEDGMENTS

I am thankful to Nootan Pharmacy College, Sankalchand Patel University, and Shri B M College of Pharmaceutical Education and Research for providing research facilities and constant motivation.

REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, *et al*. Heart disease and stroke statistics-2019 update: A report from the American Heart Association. Circulation 2019;139:e56-528.
2. Israili ZH, Hernández-Hernández R, Valasco M. The future of antihypertensive treatment. Am J Ther 2007;14:121-34.
3. Duke JA. CRC Handbook of Medicinal Herbs. 2nd ed. New York: CRC-Press; 2002.
4. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol 2014;4:1-10.
5. Kala CP, Dhyani PP, Sajwan BS. Developing the medicinal plants sector in Northern India: Challenges and opportunities. J Ethnobiol Ethnomed 2006;2:1-15.
6. Harrison DG, Marvar PJ, Titze JM. Vascular inflammatory cells in hypertension. Front Physiol 2012;3:1-8.
7. McMaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, immunity, and hypertensive end-organ damage. Circ Res 2015;116:1022-33.
8. Aggarwal S, Gurney AL. IL-17: Prototype member of an emerging cytokine family. J Leukoc Biol 2002;71:1-8.
9. Al-Nimer M, Alhussieny A. Assessment of serum interleukins17 and 1β levels in hypertensive patients treated with angiotensin converting enzyme and/or angiotensin II receptor blockers. Saudi J Health Sci 2016;5:125-9.
10. Saleh MA, Norlander AE, Madhur MS. Inhibition of interleukin 17-A but not interleukin-17f signaling lowers blood pressure and reduces end-organ inflammation in angiotensin ii-induced hypertension. JACC Basic Transl Sci 2016;1:606-16.
11. Tsoupras A, Lordan R. Inflammation, not cholesterol, is a cause of chronic disease. Nutrients 2018;10:1-38.
12. Cracowski JL, Chabot F, Labarère J, Faure P, Degano B, Schwebel C, *et al*. Proinflammatory cytokine levels are linked to death in pulmonary arterial hypertension. Eur Respir J 2014;43:915-7.
13. Agita A, Alsagaff MT. Inflammation, immunity, and hypertension. Acta Med Indones 2017;49:158-65.
14. Liu S, Dakin LA, Xing L, Withka JM, Sahasrabudhe PV, Li W, *et al*. Binding site elucidation and structure guided design of macrocyclic IL-17A antagonists. Sci Rep 2016;6:1-12.
15. Visualizer DS. Discovery Studio 3.5. San Diego, California: Accelrys Software Inc.; 2005.
16. Sanner MF. Python: A programming language for software integration and development. J Mol Graphics Mod 1999;17:57-61.
17. Kerwin SM. Diastereoselective encapsulation of tartaric acid by a helical aromatic oligoamide. J Am Chem Soc 2010;132:2466-7.

18. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010;31:455-61.
19. Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem 2015;58:4066-72.
20. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017;7:42717.