



Mechanistic Validation of an Ergogenic *T. arjuna* Standardized Extract (Oxyjun®) Using a Molecular Docking Approach

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The bark of the tree *Terminalia arjuna* commonly referred as Arjuna is widely used in Ayurveda as a therapeutic agent for heart disease. More recently, a proprietary botanical extract of *T. arjuna* with tradename, Oxyjun®, demonstrated cardiogenic and ergogenic benefits for the first time in a younger and healthier population. However, the mechanism of action and biological actives of this novel sports ingredient were not clear. A molecular docking approach was adopted to understand the protein-ligand interactions and establish the most probable mechanism(s) of cardio vascular actions of the phytoconstituents of the *T. arjuna* standardized extract (TASE). Twenty-one phytochemicals (ligands) were chosen from Arjuna and their binding affinities against eight proteins serving cardiovascular functions (target proteins) were investigated. Autodock Vina was used to carry out the molecular docking studies. Potential efficacy in humans was assessed on the basis of ADMET properties and Lipinski's Rule of 5. We found that arjunic acid, arjungenin, arjunetin, arjunglucoside1, chrysin, kaempferol, luteolin, rhamnetin and taxifolin demonstrated good docking scores and bioactivity.

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1. INTRODUCTION

Identification and quantification of one or more biologically active constituents is desirable for maintaining quality of commercially supplied plant extracts for the dietary supplement and natural products industry. However, bioactivity-guided fractionation and characterization of most potent compounds is typically elaborate and expensive especially if the plant extract is newly developed or if the claimed biological activity is novel. Molecular docking or computer-aided (in silico) studies can provide an easier start to subsequent in vitro or in vivo definitive investigations. Preparations from the bark of the Indian tree *Terminalia arjuna* have been used in traditional medicine for heart disease. Further the cardio-protective role of Arjuna has been studied more recently by several groups [1-5]. Oxyjun®, a *T. arjuna* standardized extract (TASE), was however developed by Enovate Biolife, Mumbai India, for use in sports nutrition mainly pre-workout formulas, for healthy adults of all age groups, not just cardiac patients. Girandola and Srivastava, 2017 demonstrated an improvement in the left ventricular ejection fraction and other cardiac and ergogenic benefits in young active adults on a 2-month supplementation of this proprietary TASE [6]. However, the precise mechanism of action and responsible biological actives of this novel extract remain unclear. LC-MS screening of Oxyjun® had earlier reported 21 possible glycosidic and polyphenolic compounds [7,8]. Hence, we found it interesting to study the interactions between these TASE actives (ligands) and the target proteins (of cardiovascular importance) using molecular docking approach. Our work may provide some leads for further characterization of this promising heart health ingredient.

2. MATERIALS AND METHODS

2.1 Ligand Preparation

Ligands are the phytochemical moieties identified from the extract and shortlisted to study the docking properties. Twenty-one such moieties from arjuna (ligands) were shortlisted based on LCMS screen and also from literature search [7,8]. The bioactives belonged majorly to

glycosidic and polyphenolic classes. The 3D structures of selected phytochemicals were retrieved from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) in SDF format (Table 1). Hydrogens were added to the ligands and minimized using MMFF94 force field to make them stable and ready for docking studies.

2.2 Retrieval of Target Proteins and Its Preparation

Several sets of protein targets which were known to play role in cardiovascular health or physical endurance were selected based on the thorough literature. The 3D crystal structures of these proteins were retrieved from RCSB protein data bank database (<https://www.rcsb.org/>), as enlisted in Table 2. Heteroatoms as well as water molecules were removed from the protein structures. Polar hydrogens were added in the protein structures and were minimized by applying Kollman's charge. Molecular docking was performed by AutoDock Vina to check the interaction of minimized protein and ligand and to find its binding affinity or score. All the ligands were also checked for Lipinski's Rule of Five to assess whether the compounds have chemical and physical properties which make them biologically active as well as orally consumable by humans. This analysis was performed from Drulito as well as calculation of molecular properties using Molinspiration (www.molinspiration.com).

2.3 Docking Using AutoDock Vina

Grid parameters for each protein were generated to create a grid-box, which would allow free movement of ligands. Docking was performed using AutoDockVina on all the ligands which passed the Lipinski's Rule of 5 and the bioactivity scores. AutoDockVina has been proven to outperform AutoDock [9]. The results of the docked protein and ligand results in the form of binding score. The best docking poses with 0.00 RMSD were considered. The lower the binding score (negative value) the stronger is the docking or binding affinity. Hence, these binding affinities or scores represents the accuracy of binding the ligand with the protein.

Table 1. Phytoconstituents (ligands) from TASE used for the docking study

Phytoconstituents (Ligands)	Molecular formula	PubChem ID (CID)
Arjunglucoside I	C ₃₆ H ₅₈ O ₁₁	14658050
Arjungenin	C ₃₀ H ₄₈ O ₆	12444386
Arjunic acid	C ₃₀ H ₄₈ O ₅	15385516
Arjunetin	C ₃₆ H ₅₈ O ₁₀	21152828
Gallic acid	C ₇ H ₆ O ₅	370
Luteolin	C ₁₅ H ₁₀ O ₆	5280445
Kaempferol	C ₁₅ H ₁₀ O ₆	5280863
Rutin	C ₂₇ H ₃₀	5280805
Quercetin	C ₁₅ H ₁₀ O ₇	5280343
Catechin	C ₁₅ H ₁₄ O ₆	9064
Ellagic acid	C ₁₄ H ₆ O ₈	5281855
Epigallocatechin gallate	C ₂₂ H ₁₈ O ₁₁	65064
Corilagin	C ₂₇ H ₂₂ O ₁₈	73568
Butein	C ₁₅ H ₁₂ O ₅	5281222
Chrysin	C ₁₅ H ₁₀ O ₄	5281607
Epimedin_A1	C ₃₉ H ₅₀ O ₂₀	92043273
Epimedin B	C ₃₈ H ₄₈ O ₁₉	5748393
Epimedin C	C ₃₉ H ₅₀ O ₁₉	5748394
Esculetin	C ₉ H ₆ O ₄	5281416
Rhamnetin	C ₁₆ H ₁₂ O ₇	5281691
Taxifolin	C ₁₅ H ₁₂ O ₇	439533

Table 2. Target proteins serving cardiovascular & cardio-tonic functions (<https://www.rcsb.org>)

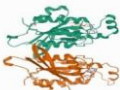


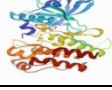
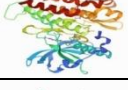



SR. No.	Target protein / ID	Structure
1	CDC42/1A4-R	
2	β-adrenergic receptors / 2RH1	
3	MAPK1/2Y9Q	
4	VEGFR1/3HNG	
5	VEGFR2/3VNT	
6	Opioid receptors(κ)/6B73	
7	Opioid receptors(δ)/6PT3	
8	PGC1 α/ 6KOT	

Table 3. Summary of binding score (kcal/mol) of the 21 ligands against the 8-target proteins

Phyto constituents (Ligands)	Protein classes							
	1A4R	2RH1	2Y9Q	3HNG	3VNT	6B73	6PT3	6KOT
Arjunetin	-6	-7.7	-7.3	-1	-7.8	5.6	7.3	-9
Arjungenin	-6.8	-7	-6.9	-3.6	-6.4	-3.6	3.3	-8.6
Arjunglucoside_1	-7	-7	-7	2.5	-7.6	5.4	6.6	-8.6
Arjunic_Acid	-7.1	-7.7	-7.1	-5.3	-6.5	-3.9	3.7	-8.8
Butein	-7.4	-9.6	-8.4	-8.8	-8.8	-8.1	-8.2	-8.4
Catechin	-6.9	-9.2	-8.9	-8.8	-8.4	-8.2	-8.1	-7.7
Chrysin	-7.2	-9.7	-8.6	-9.2	-9	-9.3	-9	-8.4
Corilagin	-6.6	-6.8	-7	0.2	-7.5	4.8	9.3	-8.8
Ellagic_Acid	-7.3	-10.3	-9.8	-7.7	-7.9	-7.5	-8	-7.4
Epigallocatechin_Gallate	-7.9	-5.6	-9.2	-7.7	-9.6	-8	-7.2	-8.5
Epimedin_A1	-5.3	-5.9	-9.8	0	-8	-0.8	5.3	-8.1
Epimedin_B	-6.1	-6.6	-10	-3.9	-9	-2.6	1.8	-9.2
Epimedin_C	-6.1	-6.4	-10.5	-3.4	-9.2	-2.3	3	-9.2
Esculetin	-6.7	-7.7	-6.9	-7.3	-6.9	-7.7	-6.6	-7
Gallic_Acid	-5.8	-6.4	-6.2	-6.1	-6.6	-6.6	-5.5	-6.2
Kaempferol	-7.3	-9.7	-9.1	-8.4	-8.8	-8.5	-9	-8
Luteolin	-7.9	-9.9	-9	-9.1	-9.1	-8.9	-9.1	-8.6
Quercetin	-7.4	-9.8	-9.1	-8.4	-9	-8.8	-9	-8.4
Rhamnetin	-7.7	-9.3	-8.9	-8.6	-9	-8.9	-9.1	-8.4
Rutin	-7.5	-6.1	-10.1	-8.4	-9.2	-7.6	-6.3	-9.2
Taxifolin	-7.3	-9.7	-9	-8.2	-8.9	-8.9	-9.1	-8.4

2.3.1 ADME profiling

ADME Profiling was performed to check the important properties such as Absorption, distribution, metabolism and excretion. Here we have used ORISIS Property Explorer to predict the logS value for all the compounds based on the SMILES notations. Bioactivity scores were predicted using the Molinspiration tool which calculates the Bioactivity score based on the structure and its functional groups present in the ligands.

2.3.2 Human efficacy predictions

Scans were carried out to determine whether the phytochemicals are likely to meet the conditions leading to efficacy in humans. Lipinski's filters using Molinspiration were applied for examining these attributes as including quantity of hydrogen acceptors, quantity of hydrogen donors, molecular weight and partition coefficient log P. The smiles format of each of the phytochemical was uploaded for the analysis.

3. RESULTS AND DISCUSSION

Autodock Vina was used to carry out the current docking studies. Autodock Vina is popular, user-friendly and vastly cited amongst the reputed publications [7]. CDC42/1A4R, β -adrenergic

receptors/2RH1, MAPK1/2Y9Q, VEGFR1/3HNG, VEGFR2/3VNT, Opioid receptors(κ)/6PT3, Opioid receptors(δ)/6PT3 and PGC1 α /6KOT) were the target proteins which were known to serve cardiovascular functions. Most of the phytoconstituents (out of 21 ligands) from *T. arjuna* demonstrated good binding affinities against selected target receptors. The data of binding energies of the selected ligands with target proteins is enlisted in Table III. Additionally, 14 ligands passed the Lipinski rule of five, proving them to be orally active.

In general, most of the ligands selected in the study have demonstrated good binding scores with decent bioactivities. Luteolin, kaempferol, catechin and chrysin, displayed higher bioactivities. The binding affinity values obtained by Autodock Vina for ligand Epigallocatechin Gallate and Luteolin for receptor CDC42 is -7.9, ligand Ellagic acid with β -adrenergic receptors is -10.3 and receptor MAPK1 is -9.8, ligand Chrysin with receptor VEGFR1 & PGC1 α is -9.2 & -9.3, ligand Luteolin with receptor VEGFR2 (3VHE & 3VNT) is -10.4 & -9.2, ligand Epigallocatechin_Gallate with receptor Opioid receptors(κ) is -9.6, ligand Luteolin, Rhamnetin, Taxifolin with receptor PGC1 α (6KOT) is -9.1, ligand Arjunic acid with receptor Opioid receptors(δ) is -8.8, respectively. Arjungenin, Arjunetin, Arjunglucoside are some of the

signature bioactives found in *T. arjuna* and in the current study they exhibited good docking scores with at least 5 of the 8 target proteins indicative of the mechanisms using which the bioactives impart the cardiovascular functions.

3.1 Molecular Docking Studies

Twenty-one ligands were checked for the docking scores with respect to different classes of proteins playing role in cardiovascular functions. The results (Table 3) suggest that phytochemicals have higher binding scores with the target proteins of cardiovascular roles. Almost all the compounds of Arjuna have a very low (negative) binding score indicating good binding. All these compounds were the top scorers in almost 8 classes of protein known to play a role in cardiovascular functions.

3.2 Bioactivity Prediction

Efficacy estimations are based on qualitative parameters that help understand acceptable a substance is, with respect to factors like bioavailability. A traditional method to evaluate pharmacological acceptability is to check compliance to Lipinski's rule of 5, which includes the numbers of hydrophilic groups, molecular weight, solubility and hydrophobicity to predict the oral bioavailability of a phytochemical [10]. It evaluates the candidate molecules for the following parameters: (a) $\text{clogP} \leq 5$; (b) Molecular weight (MW) ≤ 500 g/mol; (c) Number of hydrogen bond acceptors (sum of N and O atoms) ≤ 10 and (d) Number of hydrogen bond donors (sum of OH and NH groups) ≤ 5 [8]. Additionally, Number of rotatable bonds (nRotb) ≤ 10 and Polar surface area (PSA) $< 140 \text{ \AA}^2$, are also assessed based on additions by Veber et al (2002). The simplicity of these criteria to remove outlier molecules made them very easy to implement with the use of specific software [11,12].

Total 21 ligands were considered for screening out of which 14 ligands passed the Lipinski rule of 5, proving them to be orally active (Table 4). However, it's noteworthy that only 51% of the drugs approved by FDA are compliant to Lipinski's rule of 5 and consumed orally. Further, the biologicals and natural or semi-synthetic natural drugs which do not comply to the rule have established therapeutic effects, which means that if certain phytoconstituents violate 1 or 2 rules of Lipinski's, but demonstrate biological activities, then they should still be considered for further evaluations [13].

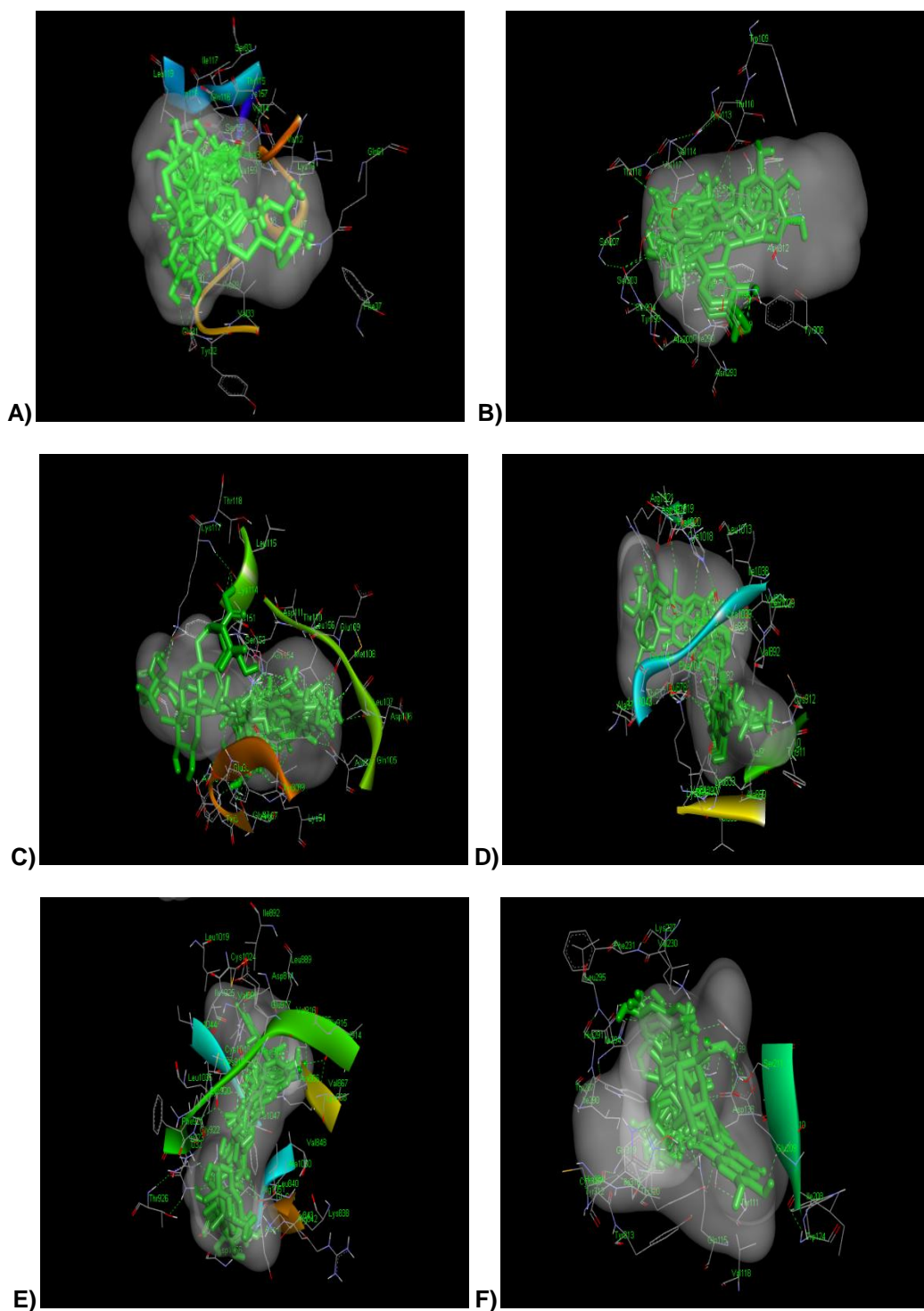
The docking studies advocate that few functions are exhibited by all these 4 bioactives, which are true to arjuna extract. Mechanisms of the cardiostimulatory functions include triggering the cascade of reactions that modulate the cardiac response to pressure overload and withstand stress or by functioning as the cardiac signaling effectors. This may be coupled with bronchodilation and smooth muscle relaxation too.

Molinspiration is a web-based tool used to predict the bioactivity scores (enlisted in Table 5) of the shortlisted potential -candidate compounds for activity with the human receptors such as GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and enzyme inhibitors [14,15]. The bioactivity scores of all the ligands can be classified into three classes – Active (>0), Moderately Active ($-5.0 - 0.0$), Inactive (< -5.0). Ligands of Epimedin_A1, Epimedin_B and Epimedin_C were not found to be biologically active based on the properties of GPCR ligand, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor and Enzyme inhibitor. Catechin, Arjunic Acid and Arjungenin showed highest bioactivity score followed by Luteolin, Quercetin, Chrysin, Kaempferol and Rhamnetin.

Quantitatively, TASE contains arjunetin, arjunglucoside-1, catechin, arjunic acid, arjungenin, luteolin, quercetin etc. arjunglucoside demonstrated good docking scores with the cell division control protein 42 (CDC42), β -adrenergic receptors, mitogen activated protein kinase-1 (MAPK1), vascular endothelial growth factor receptor-1 (VEGFR2) and peroxisome proliferator-activated receptor-gamma coactivator (PGC1 α) receptors. Thus arjunglucoside 1 acts as cardiostimulatory agent by its implications on the mechanisms involved with CDC42, which is involved in signaling effectors in the heart [16], or β -adrenergic receptors which mediate the physiologic responses such as smooth muscle relaxation and bronchodilation [17]. MAPK1 acts by initiating the cascade of signaling reactions that modulate the hypertrophic response of the heart to pressure overload [18], while VEGFR2 and PGC1 α are known to act by improving the epithelial function of the major vasculatures and enhancement of mitochondrial efficiency of cardiomyocytes, respectively [19]. Opioid receptors are known to be involved in enhancing the heart's ability to withstand stress. Arjungenin and Arjunetin also impart

cardiovascular functions through multiple of the docking poses for top scoring compounds

docked at the active site have been represented below (Fig. 1).



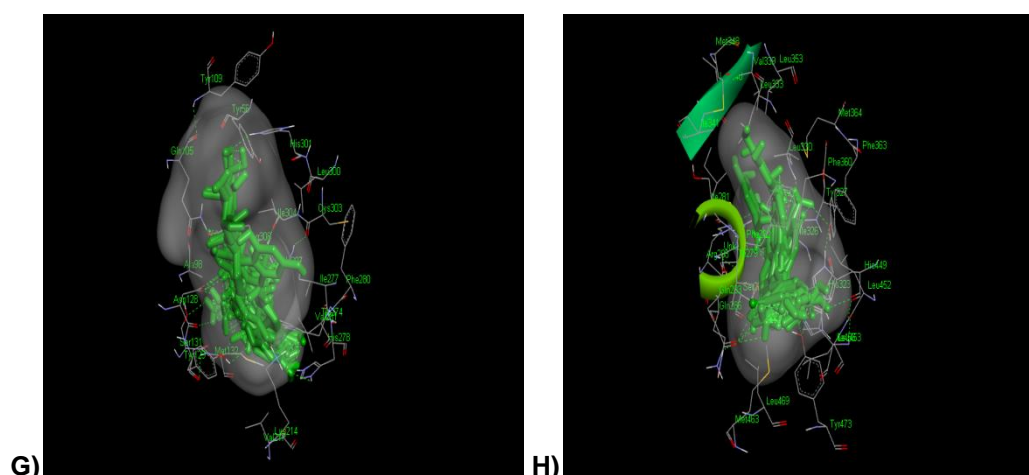


Fig. 1. Docking poses for the top scoring compounds docked at A)1A4-R, B) 2RH1, C) 2Y9Q, D) 3HNG, E) 3VNT, F) 6B73, G) 6PT3 and H) 6KOT

Table 4. Compliance of phytoconstituents (ligands) with Lipinski’s rule of 5

Phytoconstituents (Ligands)	Parameters of Lipinski’s Rule of 5 [#]						
	miLogP	TPSA	Natoms	MW	nON	nOHNH	nrotb
Arjunetin*	3.19	177.13	46	650.85	10	7	4
Arjungenin*	3.72	118.21	36	504.71	6	5	2
Arjunglucoside_I*	2.01	197.36	47	666.85	11	8	5
Arjunic_Acid	4.89	97.98	35	488.71	5	4	1
Butein	2.28	97.98	20	272.26	5	4	3
Catechin	1.37	110.37	21	290.27	6	5	1
Chrysin	2.94	70.67	19	254.24	4	2	1
Corilagin*	0.31	310.66	45	634.46	18	11	3
Ellagic_Acid	0.94	141.33	22	302.19	8	4	0
Epigallocatechin_Gallate	1.64	93.73	27	410.88	7	2	8
Epimedin_A1*	-0.26	317.36	59	838.81	20	11	12
Epimedin_B*	0.39	297.13	57	808.78	19	10	11
Epmedin_C*	0.97	297.13	58	822.81	19	10	11
Esculetin	1.02	70.67	13	178.14	4	2	0
Gallic_Acid	0.59	97.98	12	170.12	5	4	1
Kaempferol	2.17	111.12	21	286.24	6	4	1
Luteolin	1.97	111.12	21	286.24	6	4	1
Quercetin	1.68	131.35	22	302.24	7	5	1
Rhamnetin	2.22	120.36	23	316.26	7	4	2
Rutin*	-1.06	269.43	43	610.52	16	10	6
Taxifolin	0.71	127.44	22	304.25	7	5	1

miLogP- Octanol-water partition coefficient logP, TPSA-Topological polar surface area, Natoms-number of atoms, MW-molecular weight, nON-number of Oxygen Nitrogen, nOHNH-number of OH and NHn, nrotb-number of rotatable bonds and violations: number of rules violated; *: ligands that violated the Lipinski’s Rule of 5

Table 5. Bioactivity scores of the selected phytoconstituents (ligands) from Arjuna

Phytoconstituents (Ligands)	Bioactivity scores					
	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Arjunetin	-0.058	-0.917	-0.738	-0.022	0.086	0.095
Arjungenin	0.195	-0.229	-0.352	0.826	0.224	0.609
Arjunglucoside_	-0.175	-1.092	-0.846	-0.152	0.034	-0.012
Arjunic_Acid	0.237	-0.158	-0.384	0.839	0.221	0.6
Butein	-0.072	-0.108	-0.26	0.071	-0.273	0.114
Catechin	0.409	0.137	0.087	0.599	0.26	0.467
Chrysin	-0.106	-0.078	0.153	0.296	-0.303	0.262
Corilagin	-0.111	-0.707	-0.447	-0.441	-0.028	-0.15
Ellagic_Acid	-0.29	-0.266	-0.007	0.108	-0.178	0.165
Epigallocatechin_Gallate	-0.208	-0.529	-0.293	-0.364	-0.309	-0.281
Epimedin_A1	-2.129	-3.272	-2.872	-2.828	-1.661	-2.347
Epimedin_B	-1.703	-2.998	-2.493	-2.543	-1.342	-1.867
Epimedin_C	-1.91	-3.154	-2.7	-2.672	-1.481	-2.127
Esculetin	-1.046	-0.608	-1.06	-0.812	-1.167	-0.224
Gallic_Acid	-0.77	-0.255	-0.884	-0.519	-0.94	-0.173
Kaempferol	-0.1	-0.214	0.212	0.323	-0.272	0.264
Luteolin	-0.019	-0.067	0.259	0.388	-0.218	0.278
Quercetin	-0.06	-0.19	0.275	0.356	-0.248	0.28
Rhamnetin	-0.11	-0.272	0.214	0.274	-0.274	0.201
Rutin	-0.046	-0.518	-0.136	-0.233	-0.066	0.124
Taxifolin	0.086	0.025	-0.039	0.293	0.046	0.292

Athletic performance is reflection of endurance, which in turn is dependent on the cardiac health in terms of cardiac output. Steroids, hormones, erythropoietin are some of the options an athlete resorts to, which are illegal and unsafe for usage. Oxyjun® is a unique product, formulated for cardio-tonic benefits, supplementation of which, led to increased Left ventricular ejection fraction (LVEF), which is one of the key determinants of heart functioning and is directly related to the cardiac output. The supplementation also demonstrated significant increase in time to exhaustion. A study by Oberoi and co-workers, [20] demonstrated the cardio-tonic effects of water extracts of *T. arjuna* bark, most likely by enhancing the mitochondrial and sarcoplasmic reticulum health [1]. Particularly with arjuna extracts, *in silico* studies have been used to prove the cardioprotective role of *T. arjuna* bioactives in experimental diabetes [21] and α -amylase inhibition potential of arjuna stem bark extract [22]. Anti-oxidant, anti-cholinesterase and anti-amyloidogenic activities of *T. chebula* and *T. arjuna* have been studied using the molecular docking methodology [23]. Molecular docking approach has been adopted for understanding the key target protein interaction in various other diseases like dengue fever (NS4B and DENV 4)[24], breast cancer [25], HIV [26], hepatitis [27], including the recent SARS Covid 2 infection [28].

4. CONCLUSION

The docking scores, analysis of the interactions of the compounds suggest that most of the bioactives selected in this study, have the ability to bind to multiple targets involved in cardiovascular functions. Thus, this *in silico* study on the compounds of TASE indicates that compounds such as arjunic acid, arjungenin, arjunetin, arjunglucoside1, chrysin, kaempferol, luteolin, rhamnetin and taxifolin could be used as potential markers for biological activity. However, further *in vitro*, *in vivo* and quantification studies may be attempted to further establish the key bioactives in Oxyjun® that are claimed to benefit heart health and sports performance or their molecular and cellular roles.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products.

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It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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