In Silico Molecular Docking of *Salvadora Persica* Metabolites with Myocarditis Causative Coxsackie Virus B3 Capsid Proteins

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ABSTRACT

Infectious diseases caused by viruses, bacteria, and fungi have been a significant concern for human civilization since ancient times. The intracellular proliferative features of viruses set them apart from all other infectious agents. Over the past decade, more cases of RNA virus diseases have been reported than DNA viruses. Among all RNA viruses, myocarditis-causative Coxsackie virus B3 (CVB3) grabbed the attention of drug discovery scientists due to its unique infective ability of cardiomyocytes. Due to the steep rise in myocarditis incidents, the present study was designed to screen blood-brain barrier permeable efficient *Salvadora persica* metabolites that can block the entry of CVB3. In the current *in-silico* study, we adopted Swiss ADME, trRosetta, PROCHECK, Galaxy, PyRx, and Biovia Discovery Studio to screen potent binding metabolites towards VP1 and VP2 of CVB3. During Swiss ADME analysis, we screened forty *Salvadora persica* metabolites and found BBB permeable methoxybenzoic acid and umbellone. While conducting molecular interaction analysis, it was also noticed that methoxybenzoic acid showed a superior binding affinity of -4.8 towards VP1, and umbellulone exhibited a binding affinity of -5.8Kcal with VP2. Based on our studies, we inferred that BBB permeable methoxybenzoic acid and umbellone are the potential phytotherapeutics to be explored *in-silico*, *in-vitro,* and *in-vivo* data generation, essential for the management of myocarditis.

Key Words: *Plant metabolites, In-silico, Binding studies, CVB3VPs, Pre-clinical studies*

INTRODUCTION

Infectious diseases that are caused by viruses, bacteria, and fungi have been well-known to human civilization since ancient times. Researchers were drawn to viruses because of their unique obligatory intracellular proliferative characteristics. The infections caused by corona, human immunodeficiency, nipah, hanta, herpes simplex, chikungunya, human entero, dengue, Japanese encephalitis, influenza, chandipura, buffalopox, crimeancongo, and other viruses affected human health for the past few decades [1]. Currently, along with these existing viruses, coxsackie virus B3 (CVB3), a serotype of

coxsackie virus responsible for myocarditis, has been turning into a global burden.

Myocarditis is an inflammation of the myocardium that can be caused by either infectious or non-infectious agents. It is estimated that around 1.8 million cases of myocarditis occur annually worldwide, with a global prevalence range of 10.2 to 105.6 cases per 100,000 individuals [2]. Acute myocarditis is caused by the Coxsackie B3 virus. CVB3 possesses a symmetrical icosahedral capsid that holds a positive sense RNA genome. The capsid is composed of twelve pentamers, each made up of asymmetrical units of structural proteins VP1-VP4. In order to stabilize the capsid pentamers throughout the virus assembly process,

VP4, which is located on the inner surface of the shell, links the N-termini of different capsid proteins to the viral RNA. VP1, VP2, and VP3 work together to create the viral shell [3]. Among all the characteristics, the ability to bind to the Coxsackie virus and the adenovirus receptor (CAR), which are present on the transmembrane of cardiomyocytes and are crucial in coupling neighboring cardiomyocytes, attracted the interest of drug discovery scientists who wanted to create therapeutics that targeted the viral capsid subunit and infiltrated the CVB3 without harming the host biological system.

Over the past few decades, with the advent of science and technology, drug discovery scientists discovered a large number of expensive synthetic antiviral therapeutics, viz., abacavir, amprenavir, atazanavir, baricitinib, chloroquine, darunavir, didanosine, delavirdine, efavirenz, emtricitabine, favipiravir, indinavir, lamivudine, lopinavir, maraviroc, nevirapine, nelfinavir, remdesivir, ritonavir, stavudine, saquinavir, tipranavir, tenofovir, disoproxil fumarate, and zidovudine that are effective against diverse lethal infectious viral diseases [4]. Nevertheless, in addition to their therapeutic potential, these synthetic drug leads have been documented to induce numerous undesirable consequences [5]. In some instances, the antiviral agents may become ineffective in evolving virally resistant strains. With the steep rise in viral infections, the gap between production and demand for cost-effective, safe therapeutics increased drastically. Researchers began investigating transdisciplinary in silico, in vitro, and in vivo innovative ways to close the gap and help generate highly bioavailable, cost-effective, and target-specific synthetic and plant-derived antiviral medications within a set time frame.

During exploration, researchers found that the immune response modulating plant-derived metabolites can impede viral proliferation effectively without altering the host biological processes. With the advent of ethnopharmacology, researchers developed a vast number of phytotherapeutics from medicinal plants such as *Achillea fragrantissima, Aegle marmelos, Aloe vera, Andrographis paniculata, Artocarpus integrifolia, Balanites aegyptiaca, Camellia sinensis, Capparis spinosa, Cassinexylocarpa, Cistus incanus, Dioscorea bulbifera, Echinacea augustofolia, Echinacea pallid, Echinacea purpurea, Glycyrrhiza uralensis, Lindera chunii, Nicotiana benthamiana, Phyllanthus emblica, Plantago major, Wistaria floribunda,* and *Xanthocerassorbifoli* [6].Compared to all explored plants, the *Salvadoraceae* family grabbed the attention of ethnopharmacologists due to their unique bioactive metabolite's availability and adaptability to arid environments. Among all the species of *Salvadoraceae* family *Salvadora persica* phytochemicals, salvadorine,

salvadoricine, trimethylamine, benzyl isothicyanate, and other flavonoids and steroids are extensively utilized in traditional and modern medicine to treat scabies, piles, leukoderma, asthma, cough, diabetes, and sexually transmitted bacterial and viral diseases because of their high bioavailability [7]. Although scientists have revealed the mechanism of action of *Salvadora persica* phytochemicals in communicable and noncommunicable diseases using cheminformatics, genomics, and proteomics approaches, knowledge of the mechanism of action on viral myocarditis is limited.

As a result, in the current study, we used various in silico screening strategies to identify powerful blood-brain barrier-crossing anti-Coxsackie B3 virus phytochemicals from *Salvadora persica*. We are certain that the collected results will be useful for undertaking *in vitro* and *in vivo* research to create preclinical and clinical data, which is required for the development of phytotherapeutics to treat CVB3-induced myocarditis.

MATERIALS AND METHODS

The *in-silico* screening study was conducted utilizing a Lenovo laptop equipped with an 11th-generation Intel(R) Core (TM) i3 processor and 8GB of RAM. The Swiss ADME web tool was utilized for ADME investigations. The PyRx and Biovia Discovery Studio software were utilized for the preparation of the target, ligand, followed by docking and visualization.

Preparation of ligands
The reference drugs Pleconaril, 2-Fucosyllactose, and *Salvadora persica* phytochemicals 3D structure were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format. The list of all the compounds with their unique CID is as follows: Beta-sitosterol (CID:222284); Glucotropaeolin (CID:9573945); Trimethylamine (CID:1146); Methoxy benzoicacid (CID:11461); Sinigrin (CID:23671158); Myristicin (CID:4276); Myrcene (CID:31253); Longifolene (CID:289151); Benzyl isothicyanate (CID:2346); Salvadourea (CID:18509381); Umbellulon (CID:91195); Benzaldehyde (CID:240); Beta-Elemene (CID:6918391); 3-Carene (CID:26049); Terpinolene (CID:11463); Humulene (CID:5281520); gamma-Muurolene (CID:12313020); alpha-Pinene (CID:6654); beta-Pinene (CID:14896); beta-Caryophyllene (CID:5281515); Camphene (CID:6616); Limonene (CID:22311); Myristic acid (CID:11005); Lauric acid (CID:3893); Palmitic acid (CID:985); Oleic acid (CID:445639); Liriodendrin (CID:21603207); Syringin (CID:5316860); 1-Triacontanol (CID:68972); 1-Octacosanol (CID:68406); Salvadoraside (CID:162343330); Salvadoside (CID:23664985); beta-

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sitosterol-3-O-beta-d-glucoside (CID:12309057); Liriodenine (CID:10144); 12-ethylidene-8,14-diazapentacyclo octadeca-2,4,6,17-tetraen-18-yl methanol (CID:14526586); Kaempferol (CID:5280863); Quercetin (CID:5280343); Normavacurine (CID:11969908); Rutin (CID:5280805); Quercitrin (CID:5280459) [8] and the standard antiviral drugs are Pleconaril (CID:1684) and 2-fucosyllactose (CID:170484) [9, 10]. The ligands were prepared by using PyRX software and used for further analysis.

ADME and drug-likeliness properties
Swiss ADME (http://www.swissadme.ch) is a low-cost online tool for assessing the pharmacokinetics, drug-likeness, medicinal chemistry, and compatibility of small compounds. ADME/T analysis is used in drug development to evaluate the absorption, distribution, metabolism, excretion, and toxicity of a specific ligand or chemical molecule. This technique is used to eliminate unwanted compounds that lack strong drug-like properties. The Swiss ADME online tool is used to analyze the pharmacological and physicochemical characteristics of chosen compounds or hits based on their canonical SMILES. Important criteria for pharmacological validation include molecular weight, hydrogen bond acceptor and donor, topological polar surface area (TPSA), LogS, blood-brain barrier penetration, and gastrointestinal absorption [11]. The efficient lead compounds that passed ADME are being investigated for in silico docking and interaction investigations.

Preparation of the target protein
The Coxsackie virus VP1 and VP2 capsid protein sequences, which play a critical role in adhesion to CAR receptors of the host system, were obtained from the National Center for Biotechnology Information (NCBI) with accession numbers 1JEW_1 and 1JEW_2, respectively. To build the tertiary structure of proteins essential for docking studies, the VP1 and VP2 protein sequences were submitted to the trRosetta web server [12]. To assess the stereo chemical stability of the proteins, the obtained structures were subjected to the PROCHECK web server, and loop modeling was performed to obtain the maximum residues in favorable regions by using the Galaxy loop interphase of the Galaxy web server and revalidated by the PROCHECK web server [13, 14]. The active site prediction web server tool (http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp) was used to predict the active sites of the refined protein model. The selected target structures were used for *in-silico* analysis.

Molecular docking analysis
Docking assays were done using PyRx software to examine the binding affinity of ADME-passed ligands Umbellulon, Benzyl Isothiocyanate, Myrcene, Lauric Acid, and Methoxybenzoic Acid to VP1 and VP2. The ligands with the highest binding energy were then utilized to conduct molecular interaction analysis with Biovia Discovery Studio [15-17].

RESULTS AND DISCUSSION

ADME and drug-likeliness
Swiss-ADME predicts pharmacological efficacy by considering absorbability, bioavailability, site of action, metabolism, and excretion. Swiss-ADME tests were carried out on forty chosen phytochemicals from Salvadora persica. The notable features such as blood-brain barrier (BBB) permeation, gastrointestinal absorption, Lipinski's rule of five, including high oral bioavailability, polar surface area, and the presence of hydrogen bond acceptor and donor are considered for the selection of the best leads for docking given screening anti-Coxsackievirus therapeutics. The collected findings are presented in **Table 1**. The ADME cleared five blood-brain barrier crossing leads were processed for further study. During the study, it was also discovered that the BBB-permeable five molecules did not inhibit five major isoenzymes, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, which play important roles in the maintenance of cellular homeostasis and pharmacokinetics-related drug-drug interactions [18].

Table 1. ADME profile of phytochemicals

Molecules	Molecular formula	Molecular weight	Rotatable bonds	H-acceptor	H-donor	TPSA	Consensus LogP	Solubility	GI absorption	BBB permeability	Pgp substrate	Inhibitors	Lipinski violation	Bioavailability score
Beta-sitosterol	C29H50O	414.7	6	1	1	20.2	8.02	Poorly soluble	Low	No	No	No	1	0.55
Glucotropaeolin	C14H19NO9S2	409.43	7	10	5	199.79	-0.5	Yes	Low	No	Yes	No	0	0.11
Trimethyl amine	C3H9N	59.11	0	1	0	3.24	0.34	Yes	Low	No	No	No	0	0.55

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Methoxy benzoic acid	C8H8O3	152.15	2	3	1	46.53	1.49	Yes	High	Yes	No	No	0	0.85
Sinigrin	C10H17NO9S2	359.37	7	10	5	199.79	-1.27	Yes	Low	No	Yes	No	0	0.11
Myristicin	C11H12O3	192.21	3	3	0	27.69	2.49	Yes	High	Yes	No	Yes	0	0.55
Myrcene	C10H16	136.23	4	0	0	0	3.43	Yes	Low	Yes	No	No	0	0.55
Longifolene	C15H24	204.35	0	0	0	0	4.5	Yes	Low	No	No	Yes	1	0.55
Benzyl isothiocyanate	C8H7NS	149.21	2	1	0	44.45	2.91	Yes	High	Yes	No	No	0	0.55
Salvadourea	C17H20N2O3	300.35	8	3	2	59.59	2.5	Yes	High	Yes	No	Yes	0	0.55
Umbellulon	C10H14O	150.22	1	1	0	17.07	2.16	Yes	High	Yes	No	No	0	0.55
Benzaldehyde	C7H6O	106.12	1	1	0	17.07	1.57	Yes	High	Yes	No	Yes	0	0.55
Beta-Elemene	C15H24	204.35	3	0	0	0	4.65	Yes	Low	No	No	Yes	1	0.55
3-Carene	C10H16	136.23	0	0	0	0	3.42	Yes	Low	Yes	No	Yes	1	0.55
Tercinolene	C10H16	136.23	0	0	0	0	3.4	Yes	Low	Yes	No	Yes	0	0.55
Humulene	C15H24	204.35	0	0	0	0	4.26	Yes	Low	No	No	Yes	1	0.55
Gamma-Muurolene	C15H24	204.35	1	0	0	0	4.17	Yes	Low	No	No	Yes	1	0.55
Alpha-Pinene	C10H16	136.23	0	0	0	0	3.44	Yes	Low	Yes	No	Yes	1	0.55
Beta-Pinene	C10H16	136.23	0	0	0	0	3.42	Yes	Low	Yes	No	Yes	1	0.55
Beta-caryochyllene	C15H24	204.35	0	0	0	0	4.24	Yes	Low	No	No	Yes	1	0.55
Camphene	C10H16	136.23	0	0	0	0	3.43	Yes	Low	Yes	No	Yes	1	0.55
Limolene	C10H16	136.23	1	0	0	0	3.35	Yes	Low	Yes	No	Yes	0	0.55
Myristic acid	C14H28O2	228.37	12	2	1	37.3	4.45	Yes	High	Yes	No	Yes	0	0.85
Lauric acid	C12H24O2	200.32	10	2	1	37.3	3.51	Yes	High	Yes	No	No	0	0.85
Palmitic acid	C16H32O2	256.42	14	2	1	37.3	5.2	Yes	High	Yes	No	Yes	1	0.85
Oleic acid	C18H34O2	282.46	15	2	1	37.3	5.65	Poorlysoluble	High	No	No	Yes	1	0.85
Liriodenedrin	C34H46O18	742.72	12	18	8	254.14	-1.85	Yes	Low	No	Yes	No	3	0.17
Syringin	C17H24O9	372.37	7	9	5	138.07	-0.48	Yes	Low	No	No	No	0	0.55
1-Triaconcanol	C30H62O	438.83	28	1	1	20.23	10.92	Poorlysoluble	Low	No	Yes	No	1	0.55
1-Octacosanol	C28H58O	410.8	26	1	1	20.23	10.14	Poorlysoluble	Low	No	Yes	No	1	0.55
Salvadoraside	C34H48O18	744.74	14	18	9	265.14	-2.38	Yes	Low	No	Yes	No	3	0.17
Salvadoside	C13H18O9S	350.34	6	9	4	151.13	-0.7	Yes	Low	No	No	No	0	0.11
Beta-sitisterol-3-O-Beta-d-glucoside	C35H60O6	576.86	9	6	4	99.38	5.85	Poorlysoluble	Low	No	No	No	2	0.55
Liriodenine	C17H9NO3	275.26	0	4	0	48.42	2.88	Yes	High	Yes	Yes	Yes	0	0.55
12-Ethylidene-8,14-diazapentacyclo octadeca-2,4,6,17-tetraen-18-yl methanol	C19H22N2O	294.39	1	2	2	35.5	2.41	Yes	High	Yes	Yes	Yes	0	0.55
Kaempserol	C12H24O2	200.32	10	2	1	37.3	3.51	Yes	High	Yes	No	No	0	0.85
Quercetin	C15H10O7	302.24	1	7	5	131.36	0.63	Yes	High	No	No	Yes	0	0.55
Normavacurine	C19H22N2O	294.39	1	2	1	28.4	2.41	Yes	High	Yes	Yes	Yes	0	0.55
Rutin	C27H30O16	610.5	6	16	10	266	-1.3	Soluble	Low	No	Yes	No	3	0.17
Quercitrin	C21H20O11	448.38	3	11	7	190.28	0.22	Yes	Low	No	No	No	2	0.17

Structure validation

To check the quality of VP1 and VP2 protein tertiary structures obtained from trRosetta, the predicted model was initially subjected to the PROCHECK analysis. After analysis out of five models generated, the structure showing a percentage of favorable region of 89.3% for VP1 and 87.9% for VP2 was noticed and used for further analysis. To make the protein more stereochemically active, loop modeling was performed by using the Galaxy web server. Based on our *insilico* data analysis, it was noticed that the favorable region was 89.7% for VP1 and 87.9% for VP2 (**Figures 1 and 2**). This data indicates that after loop modeling, more stable structures were obtained, which are essential for *in-silico* binding affinity studies.
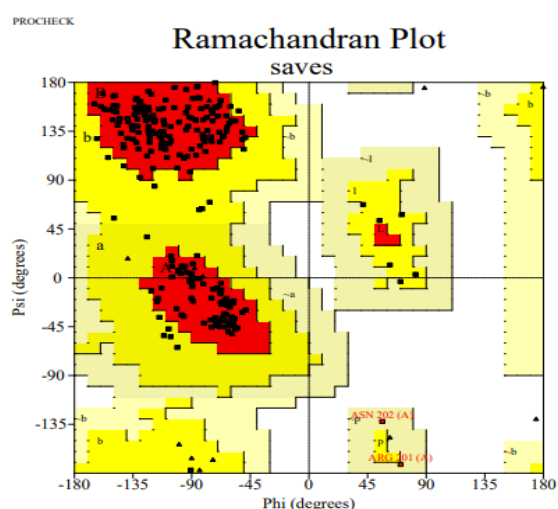
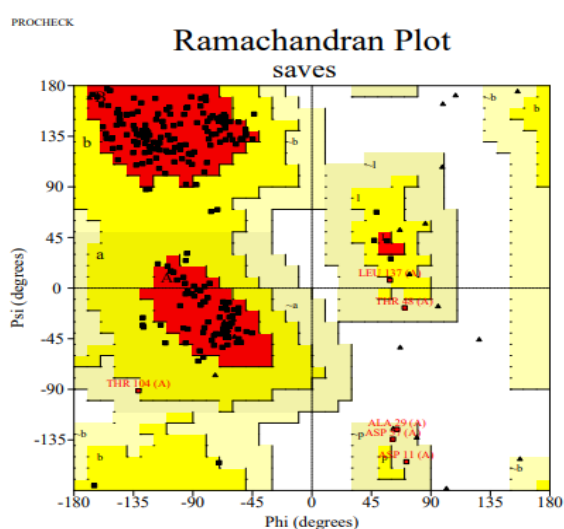**Figure 1.** Ramachandran plot of VP2 after loop modelling

Figure 2. Ramachandran plot of VP2 after loop modelling

Molecular docking and visualization

In virtual screening techniques, molecular docking is frequently employed to reduce massive libraries showing low binding affinity towards the receptor or target [19, 20]. This will also help drug discovery and development scientists conduct the *in-silico, in-vitro,* and *in-vivo* experiments cost-effectively in the stipulated time [21]. To explore the binding sites that exist on VP1 and VP2 essential for docking, the validated structures were subjected to active site prediction using the active site prediction web tool. The obtained active site coordinates, 31.62, -18.28, and 42.89 for VP1 and 17.64, 4.31, and 4.26 for VP2, were used to navigate the ligands toward binding pockets of targets to obtain better docking energies. The VP1 and VP2 targets were subjected to docking; during docking, water molecules and hetero atoms were eliminated from the structures, and polar hydrogen was added to facilitate the protein-ligand docking using the Biovia Discovery Studio program.

Docking of VP1

After docking the standard medication, pleconaril was discovered to have a significant binding affinity to the VP1 capsid protein, with a docking score of -6.1 kcal/mol. The contact involved typical hydrogen bonding with cysteine 73 and valine 91, indicating molecular specificity. Another typical medication, 2-fucosylactose, has a binding affinity with the VP1 capsid protein (docking score: -4.2 kcal/mol), forming two conventional hydrogen bonds with glutamine 96 and valine 74. The binding scores for the five phytochemicals ranged from -3.7 to -4.8 Kcal/mol. Notably, methoxybenzoic acid (CID 1461) had the closest binding affinity, with a score of -4.8 kcal/mol. Furthermore, the interaction between the ligand and target protein was determined by the formation of two hydrogen bonds involving essential amino acid residues, Arginine 248 and Aspartate 194. As a result, it was discovered that 3-methoxy benzoic acid had a nearly identical binding affinity for VP1 as the conventional medication, 2-fucosylactose. The acquired findings are reported in **Tables 2 and 4**.

Docking with VP2

In the docking analysis, the standard drug pleconaril displayed a maximum binding affinity of -6.3 Kcal/mol with the VP2 capsid protein by forming the conventional hydrogen bond with isoléucine 39. In a parallel docking analysis of the second reference lead 2-fucosylactose, we also noticed that the lead molecule exhibited an almost similar binding affinity of -6.2 Kcal/mol towards the VP2 capsid protein. It was also observed that 2-fucosylactose formed five conventional hydrogen bonds with the VP2 capsid protein. This observation resonates with the overall trend, as it was noted that all five phytochemicals subjected to docking consistently yielded scores within the range of -5 to -5.8, emphasizing the uniformity in their binding affinities (**Tables 3 and 4**). Among the phytochemicals, it

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was observed that, except for myrecene (CID 31253), all the ligands bound to the target protein showcased hydrogen bond interactions, emphasizing the favorable binding characteristics of these compounds. Despite Umbellone (CID 91195) achieving a docking score of -5.8 against VP2 capsid proteins, which may seem less commendable compared to the standard drug, its distinct advantage makes it a notable candidate.
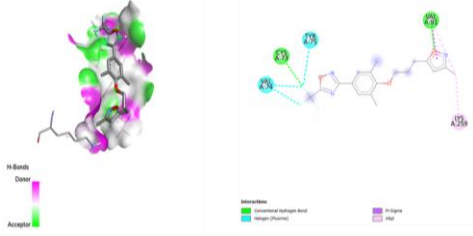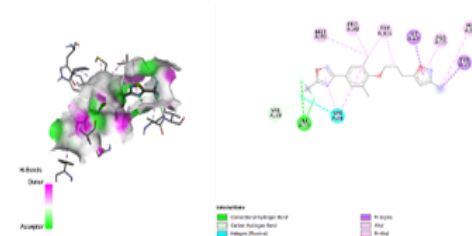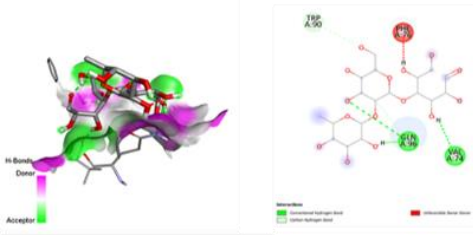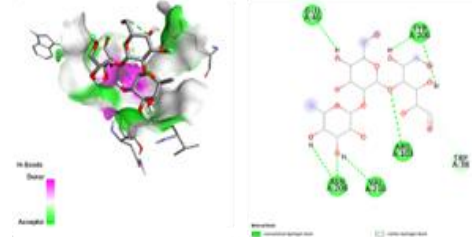
Table 2. Docking scores and amino acids involved in hydrogen bond formation between ligands and VP1

Compounds	Binding Affinity (kcal/mol)	Amino acid Residues involved in Conventional Hydrogen Bond formation
Pleconaril	-6.1	CYS-73, VAL-91
2-Fucosyl lactose	-4.2	GLN-96, VAL-74
Methoxy benzoic acid	-4.8	ASP-194, ARG-248
Myrecene	-3.7	Nil
Benzyl isothiocyanate	-4.5	Nil
Umbellulon	-4	Nil
Lauric acid	-4	VAL-74, GLN-96

Table 3. Docking scores and amino acids involved in hydrogen bond formation between ligands and VP2

Compounds	Binding Affinity (kcal/mol)	Amino acid Residues involved in Conventional Hydrogen Bond formation
Pleconaril	-6.3	ILE 39
2-Fucosyl lactose	-6.2	GLU-46, ARG-103, TYR-206, ASN-208 and VAL-210
Methoxy benzoic acid	-5.6	TYR-22, THR-24, TRP-37
Myrecene	-5.1	Nil
Benzyl isothiocyanate	-5.1	VAL-101
Umbellulon	-5.8	TRP-37
Lauric acid	-5	ALA-35 and MET-89

Table 4. VP1 and VP2 Amino Acids 2D interaction with the ligands

Ligand Name	VP1 Amino Acids 2D interaction with the ligands.	VP2 Amino Acids 2D interaction with the ligands.
Pleconaril		
2-Fucosyl lactose		

Methoxy benzoic acid

Myrecene

Benzyl isothiocyanate

Umbellulon

Lauric acid
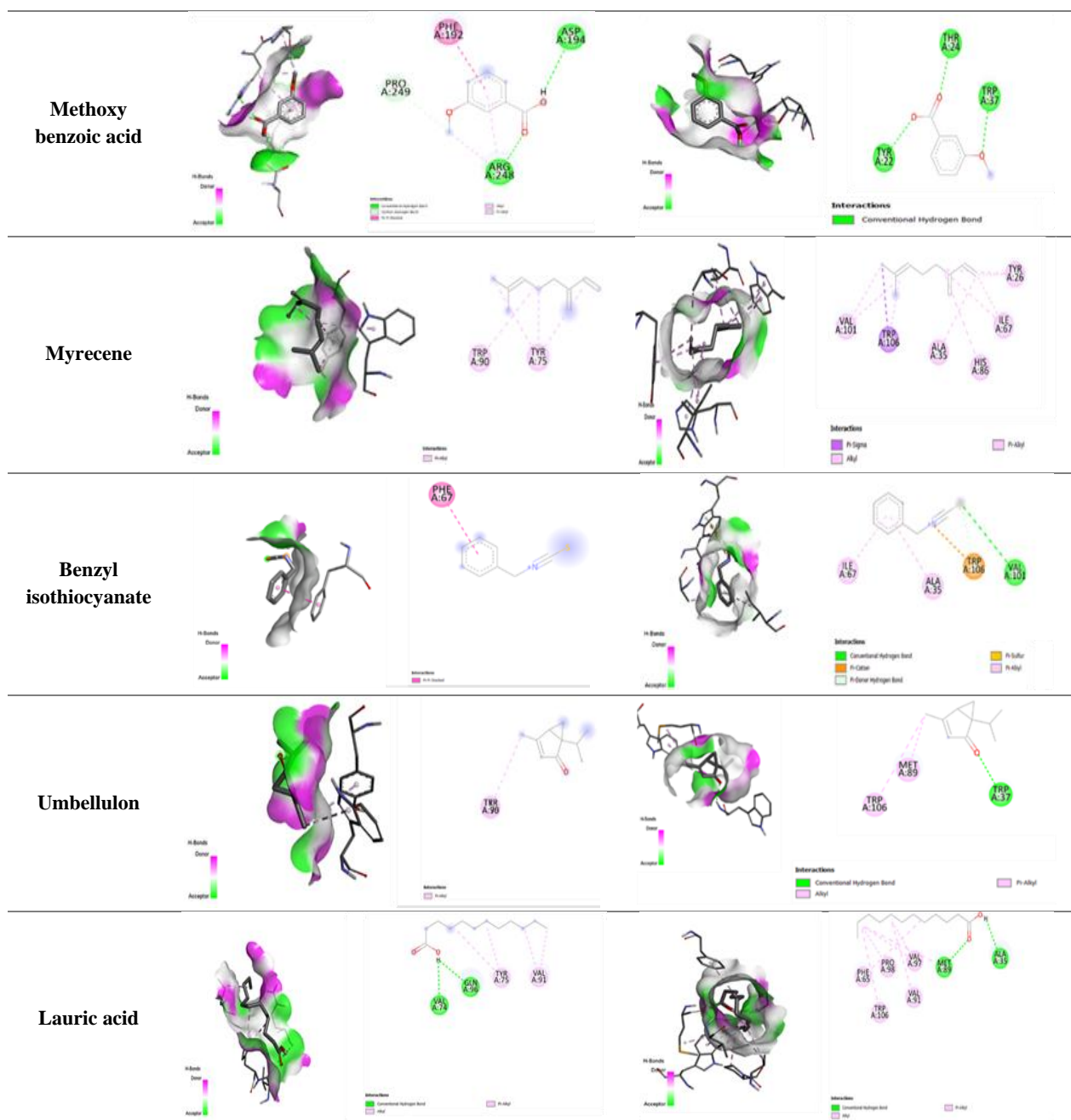
CONCLUSION

In investigating Coxsackie virus B3-induced myocarditis, our study focused on targeting the viral capsid proteins V1 and VP2, which play a pivotal role in facilitating viral entry into myocytes. Recognizing *Salvadora persica's* reported antiviral properties to inhibit the Herpes simplex virus, we conducted an *in-silico* phytochemical screening analysis to identify potential therapeutic leads essential for the management of viral myocarditis. Based on our studies, we observed that BBB permeable methoxy benzoic acid and umbellone are the potential phytochemicals to be explored *in-silico*, *in-vitro,* and *in-vivo* data generation, essential for the management of myocarditis.

REFERENCES

[1] Mani RS, Ravi V, Desai A, Madhusudana SN. Emerging viral infections in India. Proc Natl Acad Sci India Sect B Biol Sci. 2012;82(1):5-21.

[2] Golpour A, Patriki D, Hanson PJ, McManus B, Heidecker B. Epidemiological impact of myocarditis. J Clin Med. 2021;10(4):603.

[3] He Y, Chipman PR, Howitt J, Bator CM, Whitt MA, Baker TS, et al. Interaction of coxsackievirus B3 with the full-length coxsackievirus-adenovirus receptor. Nat Struct Biol. 2001;8(10):874-8.

[4] Arora G, Shrivastava R, Kumar P, Bandichhor R, Krishnamurthy D, Sharma RK, et al. Recent advances made in the synthesis of small drug molecules for clinical applications: an insight. Curr Res Green Sustain Chem. 2021;4:100097.

[5] Murugesu S, Balan T, Tamri NIM, Zamree LNH, Samba NFZ, Anuar SNHM, et al. Molecular docking analysis of christanoate and christene from christiavespertilionis plants as potential inhibitors of covid-19. Curr Trends Biotechnol Pharm. 2024;18(2):1736-44.

[6] Taïbi K, Abderrahim LA, Ferhat K, Betta S, Taïbi F, Bouraada F, et al. Ethnopharmacological study of natural products used for traditional cancer therapy in Algeria. Saudi Pharm J. 2020;28(11):1451-65.

[7] Kumar D, Sharma, PK. Traditional use, phytochemicals and pharmacological activity of *Salvadora persica*: a review. Curr Nutr Food Sci. 2021;17(3):302-9.

[8] Bader A, Flamini G, Cioni PL, Morelli I. The composition of the root oil of *Salvadora persica* L. J Essent Oil Res. 2002;14(2):128-9.

[9] Ma Y, Abdelnabi R, Delang L, Froeyen M, Luyten W, Neyts J, et al. New class of early-stage enterovirus inhibitors with a novel mechanism of action. Antiviral Res. 2017;147:67-74.

[10] Lou F, Hu R, Chen Y, Li M, An X, Song L, et al. 2'-fucosyllactose inhibits coxsackievirus class A type 9 infection by blocking virus attachment and internalisation. Int J Mol Sci. 2022;23(22):13727.

[11] 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(1):42717.

[12] Du Z, Su H, Wang W, Ye L, Wei H, Peng Z, et al. The trRosetta server for fast and accurate protein structure prediction. Nat Protoc. 2021;16(12):5634-51.

[13] Ko J, Park H, Heo L, Seok C. GalaxyWEB server for protein structure prediction and refinement. Nucleic Acids Res. 2012;40:W294-7.

[14] Laskowski RA, MacArthur MW, Thornton JM. PROCHECK: validation of protein-structure coordinates. 2006.

[15] San Diego, Dessault Systemes BIOVIA. Discovery studio modeling environment. 2021.

[16] Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Chem Biol Methods Protoc. 2015;1263:243-50.

[17] Pawar RP, Rohane SH. Role of autodock vina in PyRx molecular docking. 2021.

[18] Mishra S, Dahima R. *In vitro* ADME studies of TUG-891, a GPR-120 inhibitor using SWISS ADME predictor. J Drug Deliv Ther. 2019;9(2):366-9.

[19] Taylor RD, Jewsbury PJ, Essex JW. A review of protein-small molecule docking methods. J Comput-Aided Mol Des. 2002;16(3):151-66.

[20] Nagaraju EV. *In-silico* Prediction of anti COVID-19 therapeutics maximum binding affinity with homo sapiens acrosomal protein SP-10. Soudi J Med. 2021;7(9):469-72.

[21] Nagaraju EV. *In-silico* Prediction of maximum binding affinity of disease-modifying antirheumatic drugs with homo sapiens acrosomal protein SP-10. Int J Pharm Res Allied Sci. 2023;12(1):59-65.

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