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ORIGINAL ARTICLE

In Silico Analysis of *Cissus rotundifolia* Constituents as Human Neutrophil Elastase (HNE), Matrix Metalloproteinases (MMP 2 and MMP 9), and Tyrosinase Inhibitors

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Abstract

Cissus rotundifolia has been reported to possess various biological activities such as anti-diabetic, anti-fertility, anti-hyperlipidemic, anti-malarial, anti-osteoporotic, and anti-parasitic activities. Therefore in the present study, eleven selected constituents of *Cissus rotundifolia* which includes aconitic acid, astragalin, acteoside, aliospiroside A, beta amyrin, bergenin, formononetin, gallic acid, isovitexin, isoorientin, and isoquercitrin were studied on the docking behavior of human neutrophil elastase (HNE), matrix metalloproteinases (MMP 2 and MMP 9), and tyrosinase by using PatchDock method. Furthermore, molecular physicochemical, bioactivity score/drug-likeness, ADME (absorption, distribution, metabolism, and excretion), and toxicity analyses were also carried out using Molinspiration, Swiss ADME, and ProTox-II methods, respectively. The molecular physicochemical investigation showed that three ligands such as acteoside, aliospiroside A, and isoorientin have three violations for Lipinski's rule of five. Similarly, ADME analysis one ligand (formononetin) predicated to have high blood-brain barrier (BBB) permeability effect. The docking studies showed that isovitexin exhibited the highest atomic contact energy (−341.61 kcal/mol) for human neutrophil elastase (HNE), more over alliospiroside A has shown maximum atomic contact energy for both matrix metalloproteinases (MMP 2 [−618.00 kcal/mol] and MMP 9 [−634.73 kcal/mol]). Furthermore, isoquercitrin has exhibited the highest atomic contact energy (−145.70 kcal/mol) for tyrosinase. Thus, the present investigation outcome provides new knowledge in understanding eleven *Cissus rotundifolia* constituents as possible novel inhibitors against HNE, MMP 2, MMP 9, and tyrosinase.

Keywords Molecular docking · *Cissus rotundifolia* · Aconitic acid · Astragalin · Acteoside · Alliospiroside A

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Introduction

Cissus rotundifolia has been recognized as one of the critical essential nutritionally important species (in genus of *Cissus*) as it contains sufficient protein, fat, minerals, and vitamins [1]. Apart from nutritional property, *C. rotundifolia* has been reported to possess anti-diabetic and anti-oxidant activities [2, 3]. *C. rotundifolia* has been reported as a potential phytomedicine with analgesics, anti-inflammatory, and anti-ulcerative activities [4]. Several species of *Cissus* have been used as potential medicine in treating various diseases: for instance, (i) *C. hypoglauca* has been used for treating sore throat [5]; (ii) *C. assamica* has used as anti-venom for snake bite in China [6]; (iii) *C. quadrangularis* has used in bone fracture treatment in India and Sri Lanka [7]; and (iv) *C. rotundifolia* has been reported to possess anti-diabetic activity [8] and also consumed by all the people for preventing diabetes at an early stage.

Currently molecular docking of phytochemicals (ligands) from the medicinal plants with that of target enzymes/proteins seems to be highly beneficial in terms of identifying novel inhibitors for various deadly diseases such as COVID-19 and Alzheimer's disease [9, 10]. Molecular docking is a predominant tool in computed drug designing which helps predict the binding mode of a ligand with known target protein [11]. These in silico methodologies help in drug discovery and clinical trial research on various unexplored research areas. Interestingly, for more than two decades, there has been an increased trend in number of articles published in molecular docking [12]. The previous studies encouraged us to carry out the current research on eleven chosen *Cissus rotundifolia* constituents, which includes aconitic acid, astragalin, acteoside, alliospiroside A, beta amyrin, bergenin, formononetin, gallic acid, isovitexin, isoorientin, and isoquercitrin studied on the docking behavior of human neutrophil elastase (HNE), matrix metalloproteinases (MMP 2 and MMP 9), and tyrosinase by using PatchDock method. Furthermore, molecular physicochemical, bioactivity score/drug-likeness, ADME (absorption, distribution, metabolism, and excretion) analyses were also carried out using Molinspiration and Swiss ADME methods, respectively.

Materials and Methods

Preparation of Ligand

Chemical structures of eleven selected ligands, namely (i) aconitic acid [CID 309], (ii) astragalin [CID 5282102], (iii) acteoside [CID 5281800], (iv) alliospiroside A [CID 101641343], (v) beta amyrin [CID 73145], (vi) bergenin [CID 66065], (vii) formononetin [CID 5280378], (viii) gallic acid [CID 370], (ix) isovitexin [CID 162350], (x) isoorientin [CID 114776], and (xi) isoquercitrin [CID 5280804], were downloaded from PubMed database. The energy-minimized three-dimensional chemical structures were further used for PatchDock study.

Identification and Preparation of Target Protein

The three-dimensional (3D) structures of the HNE (PDB ID: 1H1B with resolution of 2.00 Å), MMP 2 (PDB ID: 1QIB with resolution of 2.80 Å), MMP 9 (PDB ID: 4H1Q with

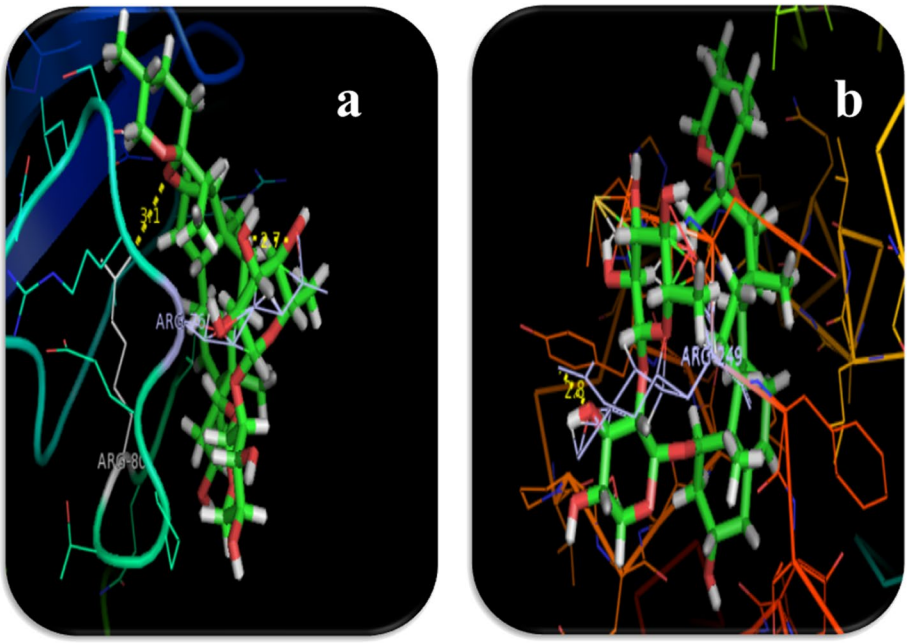

Figure 1 The interaction analysis representation of alliospiroside A with that of (**a**) human neutrophil elastase (HNE) and (**b**) tyrosinase using PyMOL software

resolution of 1.59 Å), and tyrosinase (PDB ID: 2Y9W with resolution of 2.30 Å) were obtained from the Research Collaborator for Structural Bioinformatics (RCSB) Protein Data Bank. A chain of all the target proteins was pre-processed separately by deleting other chains (B, C, and D), ligand, and crystallographically observed water molecules (water without hydrogen bonds) by using UCSF Chimera software [13].

Molecular Physicochemical and Drug-Likeness Analysis

Molecular physicochemical and drug-likeness analysis was carried out for eleven selected constituents of *Cissus rotundifolia* using the Molinspiration online tool, according to the earlier report [14].

ADME Analysis

Absorption, distribution, metabolism, and excretion (ADME) analysis was carried out for eleven selected constituents of *Cissus rotundifolia* using the Swiss ADME analysis method [15].

Toxicity Analysis

Toxicity analysis was carried out for eleven selected constituents of *Cissus rotundifolia* using the ProTox-II web server [16].

Table 1 The simplified molecular input line entry specification (SMILES) of eleven selected ligands (*Cissus rotundifolia*)

S.no	Ligand name	Simplified molecular input line entry specification (SMILES)
1	Aconitic acid	C(C(=CC(=O)O)C(=O)O)C(=O)O
2	Astragalin	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O
3	Acteoside	CC1C(C(C(C(O1)OC2C(C(OC(C2OC(=O)C=CC3=CC(=C(C=C3)O)O)CO)OCCC4=CC(=C(C=C4)O)O)O)O) O)O
4	Alliospiroside A	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(C(CC(C6)O)OC7C(C(C(CO7)O)O)OC8C(C(C(C(O8)C)O)O) O)C)C)OC1
5	Beta amyrin	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)C)C
6	Bergenin	COC1=C(C=C2C(=C1O)C3C(C(C(C(O3)CO)O)O)OC2=O)O
7	Formononetin	COC1=CC=C(C=C1)C2=COC3=C(C2=O)C=CC(=C3)O
8	Gallic acid	C1=C(C=C(C(=C1O)O)O)C(=O)O
9	Isovitexin	C1=CC(=CC=C1C2=CC(=O)C3=C(O2)C=C(C(=C3O)C4C(C(C(C(O4)CO)O)O)O)O)O
10	Isoorientin	C1=CC(=C(C=C1C2=CC(=O)C3=C(O2)C=C(C(=C3O)C4C(C(C(C(O4)CO)O)O)O)O)O)O
11	Isoquercitrin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O)O

Table 2 Molecular physicochemical analysis of eight selected (*Cissus rotundifolia*) ligands using Molinspiration web server

Ligands	Log A[1]	TPSA[2]	Natoms[3]	MW[4]	nON[5]	nOHNH[6]	Nviolations[7]	Nrotb[8]	Volume[9]
Aconitic acid	−1.22	111.90	12	174.11	06	3	0	4	137.86
Astragalin	0.12	190.28	32	448.38	11	7	2	4	364.19
Acteoside	−0.45	245.29	44	624.59	15	9	3	11	532.50
Alliospiroside A	3.04	176.77	50	708.89	12	6	3	4	658.57
Beta amyrin	8.02	20.23	31	426.73	01	1	1	0	460.70
Bergenin	−0.90	145.91	23	328.27	09	5	0	2	265.89
Formononetin	3.10	59.67	20	268.27	04	1	0	2	233.56
Isoquercitrin	−0.36	210.50	33	464.38	12	8	2	4	372.21

[1]Octanol-water partition coefficient, [2]polar surface area, [3]number of non-hydrogen atoms, [4]molecular weight, [5]number of hydrogen bond acceptors [O and N atoms], [6]number of hydrogen bond donors [OH and NH groups], [7]number of rule of 5 violations,[8]number of rotatable bonds, [9]molecular volume

Docking Studies

Docking studies were performed for eleven selected constituents of *Cissus rotundifolia* using the PatchDock online server. PatchDock uses a geometry-based molecular docking algorithm method to recognize the binding score, area, and atomic contact energy (ACE) of the given ligands. Finally, the binding site analysis was done by using PyMOL software [14].

Results and Discussion

In the genus *Cissus*, nearly 350 species have been reported throughout the world [17], of which about 13 species have been found in India. More particularly, 11 species have been found in Tamil Nadu in the Southern part of India [18]. Furthermore, six *Cissus* species, namely *C. pallida*, *C. quadrangularis*, *C. rotundifolia*, *C. setosa*, *C. trilobata*, and *C. vitiginea*, have been reported in and around Coimbatore [19]. *Cissus rotundifolia* is a climber in nature which is native to Africa and Arabian Peninsula [20] and cultivated in Egypt especially for ornamental purposes [21]. *C. rotundifolia* is generally used as food thickeners in Nigeria, and *C. rotundifolia* has been grown vastly in the southern part of Saudi Arabia especially for edible purposes [1]. *C. rotundifolia* has been traditionally used for treating various diseases like burns, diabetes, fever, gastrointestinal problems, loss of appetite, malaria, and skin diseases. Said and co-workers [21] have identified twenty-seven chemical constituents from *C. rotundifolia* using high-performance liquid chromatography (HPLC) coupled with the mass spectrometry (MS) method. Therefore, the above background encouraged us to carry out the present study where eleven selected constituents of *Cissus rotundifolia* (as shown in Table 1) were studied on the docking behavior of human neutrophil elastase (HNE), matrix metalloproteinases (MMP 2 and MMP 9), and tyrosinase by using PatchDock method.

Table 3 Drug-likeness scores of eight selected (*Cissus rotundifolia*) ligands using Molinspiration web server

Ligands	G-protein coupled receptor ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Aconitic acid	−0.52	0.09	−0.99	−0.12	−0.55	0.21
Astragalin	0.06	−0.05	0.10	0.20	−0.05	0.41
Acteoside	0.00	−0.54	−0.31	−0.24	0.06	0.00
Alliospiroside A	−0.58	−1.46	−1.44	−0.92	−0.30	−0.38
Beta amyrin	0.22	−0.05	−0.31	0.67	0.11	0.56
Bergenin	0.06	−0.09	−0.09	−0.08	−0.14	0.35
Formononetin	−0.30	−0.69	−0.19	0.05	−0.80	−0.02
Isoquercitrin	0.06	−0.04	0.13	0.20	−0.06	0.42

Table 4 Absorption, distribution, metabolism, and excretion (ADME) analysis of eight selected (*Cissus rotundifolia*) ligands using SWISS ADME web server

Ligands	GI[1]	BBB[2]	P-gp[3]	CYP1A2*	CYP2C19*	CYP2C9*	CYP2D6*	CYP3A4*	Log Kp**
Aconitic acid	High	No	No	No	No	No	No	No	−8.05
Astragalin	Low	No	No	No	No	No	No	No	−8.52
Acteoside	Low	No	Yes	No	No	No	No	No	−10.46
Alliospiroside A	Low	No	Yes	No	No	No	No	No	−9.15
Beta amyrin	Low	No	No	No	No	No	No	No	−2.41
Bergenin	Low	No	No	No	No	No	No	No	−8.99
Formononetin	High	Yes	No	Yes	No	No	Yes	Yes	−5.95
Isoquercitrin	Low	No	No	No	No	No	No	No	−8.88

[1]Gastrointestinal absorption, [2]blood-brain barrier permeant, [3]P-gp-P-glycoprotein substrate, *CYP-cytochrome P450 inhibitors, **log Kp-skin permeation (cm/s)

Table 5 Toxicity analysis of eleven selected (*Cissus rotundifolia*) ligands using ProTox-II web server

Ligand	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Aconitic acid	Inactive	Inactive	Inactive	Inactive	Inactive
Astragalin	Inactive	Inactive	Inactive	Inactive	Inactive
Acteoside	Inactive	Inactive	Active	Inactive	Inactive
Alliospiroside A	Inactive	Inactive	Active	Inactive	Inactive
Beta amyrin	Inactive	Inactive	Active	Inactive	Inactive
Bergenin	Inactive	Inactive	Active	Inactive	Inactive
Formononetin	Inactive	Active	Active	Inactive	Inactive
Gallic acid	Inactive	Active	Inactive	Inactive	Inactive
Isovitexin	Inactive	Inactive	Inactive	Active	Inactive
Isoorientin	Inactive	Inactive	Inactive	Active	Inactive
Isoquercitrin	Inactive	Inactive	Active	Inactive	Inactive

In the molecular physicochemical analysis, the violation of zero could be a significant requirement for the selected ligands. However, two ligands (acteoside and alliospiroside A) showed three violations as tabulated in the Table 2. Furthermore, it is suggested that these three ligands (aconitic acid, bergenin, and formononetin) comply well with the Lipinski's thumb rule of five.

With regard to drug-likeness property analysis of eight selected ligands (*Cissus rotundifolia*) except two ligands (alliospiroside A and formononetin), all other ligands exhibited "active" drug-likeness score towards enzyme inhibitor (descriptor) as shown in the Table 3.

Absorption, distribution, metabolism, and excretion (ADME) prediction plays a vital role in the early stage of drug discovery, screening, and design, owing to its unique characteristic nature

Table 6 The interaction energy analysis of eleven selected (*Cissus rotundifolia*) ligands with human neutrophil elastase (HNE) using the PatchDock method

Ligands	-ACE* (kcal/mol)	Interaction of amino acid residue	Bond distance (Å)
Aconitic acid	126.65	Asn61	2.8 and 3.3
Astragalin	228.28	No interactions	-
Acteoside	246.55	Arg147	3.1
		Gly193	3.3
Aliospiroside A	163.00	Arg76	2.7
		Arg80	3.1
Beta amyrin	367.66	No interactions	-
Bergenin	206.11	Asn61	2.7
		Gly193	3.4
		Ser195	3.5
Formononetin	207.77	No interactions	-
Gallic acid	6.46	Gly18	3.3
		Arg21	2.2
		Gln156	2.3
Isovitexin	341.61	His57	2.7
		Asn61	2.6
Isoorientin	384.00	Phe41	2.7
		Asn61	2.2
		Gly193	3.3
		Ser195	1.9
Isoquercitrin	154.82	Leu130	2.5
		Cys168	3.3

*-*ACE* atomic contact energy

Table 4 shows the ADME property of the eight selected ligands (*Cissus rotundifolia*) where one ligand (formononetin) is predicated on having blood-brain barrier (BBB) permeability effect.

Molecular physicochemical, drug-likeness, and ADME analysis results for three ligands, namely gallic acid, isovitexin, and isoorientin, have not been shown in the present study as reported by us earlier studies [15, 22].

The toxicity analysis of the eleven selected ligands (*Cissus rotundifolia*) is shown in Table 5, where two ligands (isovitexin and isoorientin) exhibited a mutagenicity effect.

C. rotundifolia has been reported to possess various biological activities such as analgesic, anti-bacterial, anti-inflammatory, anti-oxidant, and anti-ulcerative activities [21]. Human neutrophil elastase (HNE) is a serine protease enzyme that plays a significant role in degenerative and ant-inflammatory diseases through proteolysis extracellular matrix (ECM) components [23]. Thus, in the present study, human neutrophil elastase (HNE) was chosen as the first target protein, where the docking studies exhibited that isoorientin has the highest atomic contact energy (−384.00 kcal/mol) with that of HNE as tabulated in Table 6. In contrast, gallic acid has shown the least atomic contact energy (−6.46 kcal/mol) with that of HNE.

Table 7 The interaction energy analysis of eleven selected (*Cissus rotundifolia*) ligands with matrix metalloproteinase 2 (MMP 2) using the PatchDock method

Ligands	-ACE* (kcal/mol)	Interaction of amino acid residue	Bond distance (Å)
Aconitic acid	153.30	No interactions	-
Astragalin	333.16	Arg233	2.1
Acteoside	443.29	Ala165	3.2
		Pro215	2.4
		Ala217	2.4
Alliospiroside A	618.00	No interactions	-
Beta amyrin	437.61	No interactions	-
Bergenin	308.27	Ala217	2.4
		Thr229	3.5
Formononetin	296.43	His201	3.4
		Leu218	2.8
		Ala220	3.1
		Ile222	3.3
Gallic acid	170.53	No interactions	-
Isovitexin	374.86	Leu164	3.2
		Thr229	3.3
Isoorientin	374.95	Ala217	3.0
		Ile222	2.9
		Thr229	3.5
Isoquercitrin	445.38	Ala220	2.1
		Ile222	2.1
		Thr229	3.4

*-*ACE* atomic contact energy

Our previous study reported that both isovitexin and isoorientin have shown docking potential with that of human neutrophil elastase (HNE) using CDocker method [22]. Interestingly, two ligands (bergenin and isoorientin) showed interaction with Ser195 amino acid residue of HNE as shown in the Table 6. Similarly Fig. 1a shows the interaction of ligand (alliospiroside A) with that of HNE. However, three ligands (astragalin, beta amyrin, and formononetin) did not exhibit any interaction with amino acid residues of HNE. Beta amyrin has been reported to inhibit neutrophil elastase [24], which was good agreement which agrees with the present study. Similarly, bergenin has been reported to have anti-inflammatory activity [25].

Matrix metalloproteinases (MMPs) are a group of zinc (metal)-dependent endopeptidase that is capable of degrading extracellular matrix (ECM) components. Among the different types of MMPs, MMP 2 (72 kDa), and MMP 9 (92 kDa) were found to be increased in the disease conditions like aging, cancer, inflammation, and wound healing [23]. Thus, in the present study, MMP 2 was chosen as the second target protein. The docking studies showed that alliospiroside A has the maximum atomic contact energy (−618.00 kcal/mol) with MMP 2 as tabulated in Table 7. In contrast, aconitic acid has shown the least atomic contact energy (−153.30 kcal/mol) with MMP 2.

Interestingly, four ligands (bergenin, isovitexin, isoorientin, and isoquercitrin) showed interaction with Thr229 amino acid residue of MMP 2 as shown in Table 7. However, four ligands (aconitic acid, alliospiroside A, beta amyrin, and gallic acid) did

Table 8 The interaction energy analysis of eleven selected (*Cissus rotundifolia*) ligands with matrix metalloproteinase 9 (MMP 9) using the PatchDock method

Ligands	-ACE* (kcal/mol)	Interaction of amino acid residue	Bond distance (Å)
Aconitic acid	161.48	Asn19	3.2
		Ser364	3.1
		Lys372	2.1
Astragalin	282.04	Gln307	3.4 and 3.6
Acteoside	490.13	Gln307	3.3
		Lys376	3.4
Alliospiroside A	634.73	Trp195	3.2
		Thr197	3.5
		Lys206	1 .7
		Glu208	3.4
Beta amyrin	539.44	No interactions	-
Bergenin	325.3	Asp312	3.0
		Asp357	2.3
		Lys379	2.8 and 1.7
Formononetin	339.84	No interactions	-
Gallic acid	169.56	Asn19	3.3
		Phe368	2.2
		Lys372	2.5
Isovitexin	416.43	Gln307	2.8
		Thr308	3.1
		Asp312	2.4
		Asp357	2.2
Isoorientin	170.3	Asp312	2.9
		Glu356	2.2
		Ser364	3.1
		Lys372	3.3
Isoquercitrin	341.98	Gln44	3.3
		His178	3.3
		Lys180	3.3
		Gln196	3.5

*-*ACE* atomic contact energy

not interact with amino acid residues of MMP 2. Acetoside and formononetin have been reported to inhibit MMP 2 activity [26, 27], and similarly, our previous study reported that both isovitexin and isoorientin had shown docking potential with that of MMP 2 using the CDocker method [22].

In the present study, MMP 9 was chosen as the third target protein. The docking studies showed that alliospiroside A has the highest atomic contact energy (−634.73 kcal/mol) with MMP 9 as tabulated in Table 8. In contrast, aconitic acid has shown the least atomic contact energy (−161.48 kcal/mol) with MMP 9.

Table 9 The interaction energy analysis of eleven selected (*Cissus rotundifolia*) ligands with tyrosinase using the PatchDock method

Ligands	-ACE* (kcal/mol)	Interaction of amino acid residue	Bond distance (Å)
Aconitic acid	11.10	Pro240	2.5
		Arg249	2.5
Astragalin	27.11	Glu241	1.9
		Met247	1.9
		Arg249	2.2
		Thr251	3.3
		Leu256	2.7
Acteoside	33.54	Ala189	2.2
		Tyr245	2.4 and 2.5
		Arg249	2.9 and 3.2
Alliospiroside A	88.50	Arg249	2.8
Beta amyrin	29.60	Glu241	2.6
Bergenin	+0.80	Pro240	2.3
Formononetin	31.00	Arg249	3.3 and 3.4
Gallic acid	2.91	Leu222	2.7
		Pro240	2.5
		Glu241	2.8
		Arg249	2.9
Isovitexin	33.22	Arg249	2.9
		Pro254	2.6 and 2.1
Isoorientin	27.74	No interactions	-
Isoquercitrin	145.70	Glu241	3.3
		Ala242	3.0
		Tyr245	2.4
		Met247	3.1
		Thr251	3.0 and 3.4
		Pro254	2.5

*-*ACE* atomic contact energy

Interestingly, three ligands (astragalin, acteoside, and isovitexin) showed interaction with Gln307 amino acid residue of MMP 9 as shown in Table 8. However, two ligands (beta amyrin and formononetin) did not interact with amino acid residues of MMP 9. Acetoside and formononetin have been reported to inhibit MMP 9 activity [26, 27], and similarly, our previous study reported that both isovitexin and isoorientin had shown docking potential with that of MMP 9 using the CDocker method [22]. Moreover, astragalin has been reported to inhibit MMP 1 and MMP 3, respectively [28].

Tyrosinase is one of the rate-limiting enzymes in the biosynthesis pathway of melanin that too especially in the first two biochemical reaction steps such as (1) tyrosine hydroxylation to form 3,4-dihydroxyphenylalanine (DOPA) and (2) 3,4-dihydroxyphenylalanine (DOPA) to form dopaquinone [29]. Thus, in the present study, tyrosinase was chosen as the fourth target protein. The docking studies

showed that isoquercitrin has the highest atomic contact energy (−145.70 kcal/mol) with tyrosinase as tabulated in Table 9. In contrast, bergenin has shown the very least atomic contact energy (+0.80 kcal/mol) with that of tyrosinase. This positive atomic contract energy might be due to unfavorable interactions as reported by Castro and co-workers [30].

Interestingly, seven ligands (aconitic acid, astragalin, acteoside, alliospiroside A, formononetin, gallic acid, and isovitexin) showed interaction with Arg249 amino acid residue of tyrosinase as shown in Table 9. Similarly Fig. 1b shows the interaction of ligand (alliospiroside A) with that of tyrosinase. However, one ligand (isoorientin) did not interact with amino acid residues of tyrosinase. Acetoside and gallic acid have been reported to inhibit tyrosinase activity [31, 32].

Conclusion

In the present study, all the eleven selected ligands of *Cissus rotundifolia* showed the potential to dock with all four targeted proteins. Interestingly, alliospiroside A demonstrated the highest atomic contact energy for both matrix metalloproteinases (MMP 2 and MMP 9). In contrast, aconitic acid has shown the least atomic contact energy with MMP 2 and MMP 9. Thus, it is strongly suggested that the outcome of the present study has provided new insight of these eleven ligands of *C. rotundifolia* as potential HNE, MMP 2, MMP 9, and tyrosinase inhibitors concerning the prevention of associated disorders such as inflammation, cancer, aging, wound healing, and skin lightening.

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Author Contribution Sangeetha Mohan, Vasantha-Srinivasan Prabhakaran, and Radhakrishnan Narayanaswamy designed the research; Sangeetha Mohan, Vasantha-Srinivasan Prabhakaran, and Radhakrishnan Narayanaswamy performed the molecular docking and analyzed the results. All the authors prepared, reviewed, and submitted the manuscript.

Data Availability Not applicable

Declarations

Ethics Approval Not applicable

Consent to Participate Not applicable

Consent for Publication All authors consented to the publication of this work. Authors all confirm the permission of publication for this research work.

Competing interests The authors declare no competing interests.

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