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Original Article

Thirty-Two Selected *Cissus quadrangularis* Phytoconstituents as Modulating Agents of Human Intestinal-Type Fatty Acid Binding Protein and Carnosinase 2: An *in silico* Study

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ABSTRACT

Background and Objectives: Cissus quadrangularis (Pirandai) is well known for various biological activities. In the present investigation, we aimed to study thirty-two selected phytoconstituents of *C. quadrangularis* (Pirandai) as potent modulating agents of human Intestinal-type Fatty Acid Binding Protein (hI-FABP) and human Carnosinase 2 (hCN 2) using a docking approach. **Materials and Methods:** The thirty-two chosen constituents were studied on the docking behavior of hI-FABP and hCN 2 using the Swiss dock method. In addition to docking, toxicity analysis of 32 chosen ligands was determined using the Pro-Tox 3 online server. **Results:** Toxicity analysis predicted two ligands (3-O-Methylgallic acid and 9Z,12Z,15Z-Octadecatrienoic acid) to have cytochrome P450 1A2 inhibitory activity. Docking results revealed that Ligustrosidic acid and Linarin exhibited the highest binding energy (-9.50 and -10.01 kcal/mol) with hI-FABP and hCN 2, respectively. **Conclusion:** The findings provide new knowledge of these ligands as potent modulating agents, which will aid in managing health and well-being, particularly obesity-related disorders.

Keywords: *Cissus quadrangularis*, Docking, Good health and well-being, Human carnosinase 2, Human intestinal-type fatty acid binding protein, Pirandai.

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INTRODUCTION

Cissus quadrangularis (Pirandai) is a perennial climber plant, which belongs to Vitaceae (grape) family (Kumar *et al*., 2020). This plant has been traditionally used in Africa, Bangladesh, Cameroon, India, Sri Lanka and Thailand to treat various diseases (Sawangjit *et al*., 2017). Till date 350 *Cissus* species have been reported (Rahmawati *et al*., 2021) which includes *C. aralioides, C. assamica, C. bathyrakodes, C. cactiformis, C. cornifolia, C. hastata, C. hypoglauca, C. ibuensis, C. incisa, C. javana, C. latifolia, C. oliveri, C. quadrangularis, C. rhombifolia, C. repanda, C. repens, C. rotundifolia, C. rubiginosa, C. sicyoides, C. subtetragona, C. trifoliata, C. verticillata* and *C. vitiginea*.

Among above mentioned *Cissus* species *Cissus quadrangularis* is one of the popularly known species used for more 100 years in the Indian traditional medicine that to particularly in Ayurvedic medicine (Brahmkshatriya *et al*., 2015). The vernacular names for *Cissus quadrangularis* are "Adamant Creeper" in English, "Chodhari" in Gujarati, "Hadjod" in Hindi, "Peranta" in Malayalam, "Mangarahalli" in Kanada, "Hadavhanga" in Oriya, "Pirandai" in Tamil, "Nalleru" in Telugu, "Phet sang-Khaat" in Thai, "Asthisanghata" in Sanskrit, "Heeressa" in Sinhala, "Harjora" in Urdu (Rex and Ravi, 2020). Different plant parts of *Cissus quadrangularis* (Pirandai) are traditional used as follows i) whole plant is used to treat osteoarthritis, osteoporosis and rheumatoid; ii) both roots and stems extracts are used for repairing fractured bones and torn ligaments; iii) stem extract is used to cure epistaxis, menstrual irregularities and scurvy; iv) fresh leaves and stems are used to treat dysmenorrhea, dyspepsia, hemorrhoids and scurvy (Sawangjit *et al*., 2017; Aarthi *et al*., 2024).

Cissus quadrangularis (Pirandai) has been reported to possess various pharmacological activities such as anti-bacterial, anti-diabetic, anti-fungal, anti-inflammatory, anti-microbial, anti-obesity, anti-osteoporotic, anti-oxidant, anti-pyretic, anti-ulcer, anxiolytic, bone-healing, gastro-protective (Vinoth and Kumar, 2025).

The earlier reports motivated us to perform the current investigation on thirty two chosen constituents which

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includes i) Aglacin I, ii) Agropinic acid, iii) Alpha-amyrin, iv) Apigenin 6-C-glucoside 8-C-arabinoside, v) Apiin, vi) Atractylodin, vii) Cis-P-coumaric acid, viii) Cosmosiine, ix) 3,4-dimethoxyphenethyl alcohol, x) Dyphylline, xi) 5,8,11-Eicosatriynoic acid, xii) 2- Furancarboxaldehyde, 5-(hydroxymethyl), xiii) Gallocatechin gallate, xiv) Ginkolide B, xv) Hexadecanedioic acid, xvi) n-Hexadecanoic acid, xvii) Isoquercitrin, xviii) Kaempferol-3-o-galactoside, xix) Kaempferol 3-rutinoside, xx) Ligustrosidic acid, xxi) Linarin, xxii) Malic acid, xxiii) 3-O-Methylgallic acid, xxiv) 9Z,12Z,15Z-Octadecatrienoic acid, xxv) 2-Oxo-4-Methylthiobutanoic acid, xxvi) Phytol, xxvii) Preskimmianine, xxviii) 4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl, xxix) Quercetin-3-o-xyloside, xxx) Quercitrin, xxxi) Secologanin and xxxii) Tetradecanoic acid.

These above-mentioned *C. quadrangularis* (Pirandai) phytochemicals were aimed to investigate on the molecular docking analysis of human intestinal-type fatty acid binding protein (hI-FABP) and human Carnosinase 2 (hCN 2) by using the swissdock method, which aids in developing anti-obesity agents for managing obesity related disorders.

MATERIALS AND METHODS

Ligand preparation

The chemical structures of thirty-two selected *C. quadrangularis* (Pirandai) ligands were chosen for the current study based on earlier reports (Mehta *et al.*, 2001; Dinesh Kumar *et al.*, 2020; Kannaa *et al.*, 2022, Aarthi *et al.*, 2024; Mondal *et al.*, 2025), that includes 1) Aglacin I (CID 21578048); 2) Agropinic acid (CID 173285); 3) Alpha-amyrin (CID 73170; 4) Apigenin 6-C-glucoside 8-C-arabinoside (CID 131750832); 5) Apiin (CID 5280746); 6) Atractylodin (CID 442004); 7) Cis-P-coumaric acid (CID 1549106); 8) Cosmosiine (CID 5280704); 9) 3,4-dimethoxyphenethyl alcohol (CID 81911); 10) Dyphylline (CID 3182); 11) 5,8,11-Eicosatriynoic acid (CID 1781); 12) 2- Furancarboxaldehyde, 5-(hydroxymethyl)- (CID 237332); 13) Gallocatechin gallate (CID 5276890); 14) Ginkolide B (CID 65243); 15) Hexadecanedioic acid (CID 10459); 16) n-Hexadecanoic acid (CID 985); 17) Isoquercitrin (CID 5484006); 18) Kaempferol-3-o-galactoside (CID 5282149); 19) Kaempferol 3-rutinoside (CID 5318767); 20) Ligustrosidic acid (CID 146014676); 21) Linarin (CID 5317025); 22) Malic acid (CID 525); 23) 3-O-Methylgallic acid (CID 19829); 24) 9Z,12Z,15Z-Octadecatrienoic acid (CID 5280934); 25) 2-Oxo-4-Methylthiobutanoic acid (CID 473); 26) Phytol (CID 5280435); 27) Preskimmianine (CID 12305721); 28) 4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl- (CID 119838); 29) Quercetin-3-o-xyloside (CID 5321278); 30) Quercitrin (CID 5280459); 31) Secologanin (CID 161276); 32) Tetradecanoic acid (CID 11005) and 33) Standard drug (Orlistat) (CID 3034010) were downloaded from PubChem compound database. These thirty-two selected *C. quadrangularis* (Pirandai) structures were drawn and prepared by using ChemDraw 2D and 3D software tools. Thus, these prepared three-dimensional structures were used for further (swissdock) studies (Mohan *et al.*, 2023).

Preparation of target proteins

The 3-D [three-dimensional] structure of human intestinal-type fatty acid binding protein [hI-FABP] (PDB◊◊ ID: 3AKM with a resolution of 1.90 A°) and human carnosinase 2 [hCN 2] (PDB◊◊ ID: 4RUH with a resolution of 2.25 A°) was downloaded from *C. quadrangularis* (Pirandai) ◊◊Protein Data Bank (PDB). "A" chain of these two proteins was prepared separately by deleting other chains, ligands, and even the crystallographically observed "water" (H_2O) molecules by using UCSF Chimera software tool (Mohan *et al.*, 2023).

Toxicity analysis

Pro-Tox 3 online server was used to predict the toxicity effect of 32 selected *C. quadrangularis* (Pirandai) ligands (Mohan *et al.*, 2022).

Docking study

A docking study was performed for thirty-two selected phytoconstituents of *C. quadrangularis* (Pirandai) and one standard drug (Orlistat) with two target proteins (hI-FABP and hCN 2) using the Swissdock free web server (Prakash *et al.*, 2023). Finally, "PLIP" [Protein-Ligand Interaction Profiler] free online server was utilized to determine the binding site of best-docked pose for each ligand. Docking protocol was validated using orlistat as standard drug. And the Root Mean Square Deviation (RMSD◘) analysis of all the docked complexes [32 ligands] was separately compared with that of orlistat [standard drug] docked complex for each chosen target protein by using the "align" command in 'PyMOL' software (Ramsbottom *et al.*, 2018; Narayanaswamy *et al.*, 2024).

In present investigation, no experimental animals (or) human subjects were used, thus ethical approval was not needed.

With regard to statistical analysis, in the present study orlistat (standard drug) was used for the comparison purpose.

RESULTS

In the present investigation, Table 1 represents the toxicity analysis of thirty-two chosen *C. quadrangularis* (Pirandai) ligands, in which no hepatotoxicity was predicted by any of the ligands. Two ligands (3-O-Methylgallic acid and 9Z,12Z,15Z-Octadecatrienoic acid) of *C. quadrangularis* (Pirandai) were predicted to have cytochrome P450 1A2 inhibitory effect (as shown in Table 1).

In the present molecular docking analysis showed that Ligustrosidic acid has the Highest Binding Energy (HBE) (-9.50 kcal/mol) with the human Intestinal-Type Fatty Acid

Table 1: Toxicity analysis of thirty-two selected *Cissus quadrangularis* (Pirandai) ligands using the Pro-Tox 3 online server.

Ligand	HT[1a]	Carcino[2b]	Immuno[3c]	Mutagen[4d]	Cyto[5e]	AhR[6f]	AR[7g]	AR-LBD[8h]	Aromatase	ER[9i]	ER-LBD[9j]	PPAR-γ[□]	NRF2/ ARE[◊]	HSE[□]	MMP[◊◊]	p53[□□]	ATAD5[□]	CYP1A2[□]	CYP2C19[□]
Aglancin I	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	A"	IA'	IA'	IA'
Agropinic acid	IA'	IA'	A"	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	A"	IA'	IA'	IA'
Alpha-amyrin	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	A"	IA'	IA'
Apigenin- 6-c-glucoside 8-c-arabinoside	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Atractylodin	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Apiin	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Cis-p-coumaric acid	IA'	IA'	A"	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Cosmosiin	IA'	IA'	A"	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
3,4-dimethoxyphenethyl alcohol	IA'	IA'	A"	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Dyphylline	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
5,8,11-Eicosatriynoic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
2-Furancarboxaldehyde,5-(hydroxymethyl)	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Gallocatechin gallate	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Ginkgolide B	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Hexadecanedioic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
n-Hexadecanoic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Isoquercitrin	IA'	IA'	A"	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Kaempferol-3-o-galactoside	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Kaempferol-3-rutinoside	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Ligustrosidic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Linarin	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Malic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
3-O-Methylgallic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	A'	IA'
9Z,12Z,15Z-Octadecatrienoic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	A'	IA'
2-oxo-4- methylthiobutanoic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Phytol	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Preskimmianine	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Quercetin-3-o-xyloside	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Quercitrin	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Secologanin	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Tetradecanoic acid	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'
Orlistat	A"	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'	IA'

Note: HT1a- Hepatotoxicity, Carcino2b -Carcinogenicity, Immuno3c- Immunotoxicity, Mutagen4d -Mutagenicity, Cyto5e -Cytotoxicity, AhR6f -Aryl hydrocarbon Receptor, AR7g -Androgen Receptor, AR-LBD8h-Androgen Receptor Ligand Binding Domain, ER9i- Estrogen Receptor Alpha, ER-LBD0j- Estrogen Receptor Ligand Binding Domain, PPAR-γ □ - Peroxisome Proliferator Activated Receptor Gamma, NRF2/ARE◊-Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element, HSE°- Heat shock factor response element, MMP◊◊-Mitochondrial Membrane Potential, p53□□-Phosphoprotein (Tumor supressor), ATAD5▪-ATPase family AAA domain-containing protein 5p, CYP1A2▼- Cytochrome [CYP] P450 1A2 inhibitor, CYP2C19▲- Cytochrome [CYP] P450 2C19 inhibitor, IA'- Inactive, A"- Active.

Binding Protein (hI-FABP). In contrast, Alpha -amyrin had the lowest binding energy (LBE) (-5.70 kcal/mol) with the human Intestinal-type Fatty Acid Binding Protein (hI-FABP) (as shown in Table 2).

Twelve ligands (Agropinic acid, Cis-p-coumaric acid, Cosmosiin, 5,8,11-Eicosatriynoic acid, Gallocatechin gallate, n-Hexadecanoic acid, Isoquercitrin, Malic acid, 3-O-Methylgallic acid, Quercetin-3-o-xyloside, Quercitrin and Standard drug-Orlistat) have shown interactions with ASP 34 amino acid residue of human Intestinal-type Fatty Acid Binding Protein (hI-FABP). Similarly, twelve ligands (Agropinic acid, Cosmosiin, 5,8,11-Eicosatriynoic acid, Gallocatechin gallate, Isoquercitrin, Kaempferol-3-rutinoside, Ligustrosidic acid, Malic acid, 2-oxo-4-methylthiobutanoic acid, Quercetin-3-o-xyloside, Quercitrin and Orlistat) have shown interactions with SER 53 amino acid residue of human Intestinal-type Fatty Acid Binding Protein (hI-FABP) (as shown in Table 2). However, five ligands (Aglancin I, Alpha -amyrin, Atractylodin, Apiin and 9Z,12Z,15Z-Octadecatrienoic acid) does not shown any interaction with the amino acid residue of human Intestinal-type Fatty Acid Binding Protein (hI-FABP).

The current docking results showed that Linarin has the Maximum Binding Energy (MBE) (-10.01 kcal/mol) with the human Carnosinase 2 (hCN 2) enzyme. On the other hand, 4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl had the

Table 2: The Swissdock binding energy analysis of thirty-two chosen *Cissus quadrangularis* (Pirandai) ligands with the human intestinal-type fatty acid binding protein (hI-FABP) using Swissdock method.

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°
Aglancin I	5.91	NI▪▪	-	-
Agropinic acid	8.23	ASP34 GLU51 SER53 ARG56	1.98 1.98 2.33 and 2.42 2.48	2.94 2.91 3.23 and 3.23 3.26
Alpha -amyrin	5.70	NI▪▪	-	-
Apigenin- 6-c-glucoside 8-c-arabinoside	7.42	GLU59 THR67 ASN71 ARG79	2.07 3.06 3.12 2.63	3.04 4.09 3.62 3.56
Atractylodin	6.72	NI▪▪	-	-
Apiin	7.19	NI▪▪	-	-
Cis-p-coumaric acid	9.37	ASP34 ASP74	1.80 2.29	2.78 3.24
Cosmosiin	6.94	TYR14 ASP34 GLU51 SER53 ARG56 GLN115 ARG126	3.06 1.99 2.12 2.45 and 2.40 2.52 3.22 3.07	4.09 2.85 3.08 3.35 and 3.35 3.46 3.98 3.69
3,4-dimethoxyphenethyl alcohol	8.01	TYR14 ARG106	3.08 and 3.51 3.30	3.96 and 3.96 3.74
Dyphylline	7.76	GLU51 ARG56 TYR70 ALA73	2.02 2.70 3.48 3.42	2.99 3.45 4.03 4.05
5,8,11-Eicosatriynoic acid	8.34	ASP34 SER53	1.81 2.78	2.79 3.58

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°
2-Furancarboxaldehyde,5-(hydroxymethyl)	6.53	GLU51 ARG106	2.27 and 1.81 3.01 and 2.69	2.78 and 2.78 3.82 and 3.58
1-Fluoro-25-hydroxy-16-ene-23-yne-26 ,27-hexadeuterovitamin-D3	8.71	GLU51 ARG106	3.82 3.21	3.82 3.77
Gallocatechin gallate	8.43	TYR14 ASP34 GLU51 SER53 ARG56 TYR70 ASP74 ARG106	2.33 and 2.08 2.47 2.98 2.87 2.52 2.73 3.49 and 3.14 3.44 and 2.46	2.91 and 3.01 3.42 3.92 3.78 3.19 3.27 3.99 and 3.97 3.44 and 2.46
Ginkgolide B	6.69	VAL61 ASN71	2.20 2.28 and 3.15	3.09 3.14 and 3.56
Hexadecanedioic acid	8.69	GLU51	1.90	2.86
n-Hexadecanoic acid	6.44	ASP34 GLU51 ARG56	3.31 and 1.82 2.06 2.62	3.61 and 2.79 3.05 3.44
Isoquercitrin	8.74	ASP34 GLU51 SER53 ARG56 TYR70 ALA73 ARG106	2.83 and 2.18 2.07 2.44 2.98 and 2.34 3.12 and 3.44 3.22 2.83 and 3.23	3.68 and 3.06 3.05 3.33 3.74 and 3.26 3.44 and 3.90 4.06 3.20 and 3.83
Kaempferol-3-o-galactoside	7.84	TYR14 GLU51 ARG106 GLN115	3.11 2.05 2.81 2.57	3.54 2.96 3.27 3.05
Kaempferol-3-rutinoside	9.18	TYR14 GLU51 SER53 TYR70 ALA73 ASP74 ARG106 GLN115	3.20 2.90 and 2.59 2.74 2.64 3.40 2.59 2.80 3.35	3.84 3.80 and 3.03 3.69 3.06 4.09 3.47 3.17 3.86
Ligustrosidic acid	9.50	GLU51 SER53 ARG56 ALA73 ARG126	1.85 2.61 1.82 2.13 3.49	2.73 3.20 2.81 3.07 3.89

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°
Linarin	7.17	VAL61 ASN71 ASP74 GLY75	3.07 3.12 3.65 3.62	4.02 3.64 3.96 4.09
Malic acid	6.75	ASP34 GLU51 SER53	1.78 1.81 3.09	2.75 2.73 3.93
3-O-Methylgallic acid	6.59	ASP34	1.80	2.79
9Z,12Z,15Z-Octadecatrienoic acid	8.08	NI¨	-	-
2-oxo-4- methylthiobutanoic acid	6.71	GLU51 SER53 ARG56	1.82 2.73 3.45	2.77 3.54 4.04
Phytol	8.93	GLU51 ARG106	2.35 and 1.83 2.99 and 2.50	2.79 and 2.79 3.73 and 3.35
Preskimmianine	7.95	GLN115	2.62	3.51
4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl	6.59	GLU51 ARG106 GLN115	1.96 2.76 2.61	2.85 3.21 3.25
Quercetin-3-o-xyloside	8.87	TYR14 ASP34 SER53 TYR70 ARG126	3.12 2.67 and 1.85 2.42 2.99 2.82	4.01 3.47 and 2.72 3.25 3.34 3.18
Quercitrin	9.04	TYR14 ASP34 SER53 TYR70 ALA73 TRP82	2.71 1.93 2.52 and 2.93 2.70 3.02 3.18	3.58 2.88 3.33 and 3.87 3.16 3.97 3.49
Secologanin	8.13	TYR14 ASP74 ARG106 GLN115	3.24 3.42 and 2.80 2.74 2.81	3.92 3.86 and 3.59 3.63 3.25
Tetradecanoic acid	7.64	GLU51 GLN115	3.33 2.53	4.06 3.12
Orlistat	10.33	SER53 ARG56 TYR70	3.24 3.02 2.14	3.82 3.81 3.07

Note: NI¨-No hydrogen bond interactions.

Least Binding Energy (LBE) (-5.92 kcal/mol) with the human Carnosinase 2 (hCN 2) enzyme (as shown in Table 3).

Seven ligands (Aglancin I, Apiin, Hexadecanedioic acid, Isoquercitrin, Kaempferol-3-rutinoside, Secologanin and Orlistat) have shown interactions with ARG 211 amino acid residue of human Carnosinase 2 (hCN 2) enzyme. Interestingly, four ligands (Apigenin- 6-c-glucoside 8-c-arabinoside, 5,8,11-Eicosatriynoic acid, Ginkgolide B and Secologanin) have shown interactions with GLU 414 amino acid residue of human Carnosinase 2

Table 3: The Swissdock binding energy analysis of thirty-two chosen *Cissus quadrangularis* (Pirandai) ligands with the human carnosinase 2 (hCN 2) enzyme using Swissdock method.

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°
Aglancin I	8.56	ARG211 LEU297 LEU314	2.22 3.08 3.56	3.20 3.85 3.56
Agropinic acid	7.26	GLN67 LYS68 PRO70 GLU171 GLY379	2.14 2.84 and 1.99 3.25 2.09 and 1.84 3.03	3.06 3.53 and 2.77 3.98 2.81 and 2.81 3.42
Alpha -amyrin	7.90	NI▪▪	-	-
Apigenin- 6-c-glucoside 8-c-arabinoside	8.09	ARG308 GLU414 GLY415 ALA440 SER446	2.88 1.81 2.94 2.66 3.52 and 2.01	3.71 2.74 3.66 3.35 3.96 and 2.94
Atractylodin	6.33	NI▪▪	-	-
Apiin	9.14	ARG211 ASN263 LEU314	2.55 2.06 2.75 and 2.60	3.00 3.00 3.21 and 3.56
Cis-p-coumaric acid	8.12	SER32 GLN67 SER168 GLU320 LYS339	1.96 2.53 3.15 2.04 3.12	2.86 3.44 3.86 2.92 3.88
Cosmosiin	6.46	GLY255 LEU314 LEU316	2.40 3.20 2.94	3.11 3.95 3.80
3,4-dimethoxyphenethyl alcohol	7.99	GLU167 SER168 ARG343	1.95 3.21 2.93	2.89 4.10 3.37
Dyphylline	7.12	GLN103 HIS380	3.03 2.38	3.72 2.38
5,8,11-Eicosatriynoic acid	7.97	GLU414	1.86	2.82
2-Furancarboxaldehyde,5-(hydroxymethyl)	5.95	PHE389	2.01	2.86
1-Fluoro-25-hydroxy-16-ene-23-yne-26 ,27-hexadeuterovitamin-D3	8.61	ILE304 GLY443 ALA444	3.60 3.10 2.31	3.94 3.61 3.28

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°
Gallocatechin gallate	7.99	GLN67 SER168 GLN171 GLU219 GLU320	2.60 3.31 1.95 2.73 2.21	3.42 3.83 2.89 3.65 3.04
Ginkgolide B	7.90	ARG308 GLU414 ALA440	3.63 1.94 2.73	3.97 2.92 3.42
Hexadecanedioic acid	8.01	ARG211 GLU264	3.30 3.08 and 2.90	3.98 3.56 and 2.90
n-Hexadecanoic acid	7.11	GLU166 HIS380	1.85 2.86	2.82 3.39
Isoquercitrin	7.84	ARG211 LEU297 HIS298 SER313 SER315	2.06 and 3.24 3.13 2.89 3.42 2.89	3.00 and 3.90 4.07 3.63 3.94 3.70
Kaempferol-3-o-galactoside	8.56	GLY255 ASN256 ILE304 HIS307 PRO312 LEU314	2.29 3.20 2.98 2.67 1.88 2.40	3.02 3.79 3.61 3.41 2.75 3.31
Kaempferol-3-rutinoside	8.83	ARG211 GLY255 LEU297 HIS307 SER313 ARG343	2.24 and 2.87 2.27 2.54 3.01 3.00 2.58	3.20 and 3.67 3.20 3.42 3.63 3.43 3.28
Ligustrosidic acid	8.97	TYR197 ARG308 ALA440 ALA444	2.85 3.37 and 3.24 2.36 and 2.56 3.25 and 1.89	3.65 4.05 and 3.94 3.19 and 3.28 3.78 and 2.81
Linarin	10.01	SER32 ARG38 GLN67 SER168 GLU171 LYS375	2.16 3.29 2.20 3.12 2.42, 2.10 and 1.90 2.90	2.91 3.81 3.16 3.67 3.08, 3.08 and 2.86 3.30
Malic acid	6.17	ASP63	3.28 and 1.95	3.88 and 2.88
3-O-Methylgallic acid	6.26	GLY261 ASN263 GLN356	2.71 3.03 2.76 and 2.41	3.58 4.00 3.57 and 3.07

Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (H-A) in A°	Bond distance (D-A) in A°
9Z,12Z,15Z-Octadecatrienoic acid	7.53	ASN256 LEU297	3.54 3.24	4.08 3.68
2-oxo-4- methylthiobutanoic acid	6.99	GLU166 ARG343	1.84 2.29 and 2.87	2.81 3.02 and 3.48
Phytol	7.94	GLN103	3.55 and 1.98	4.02 and 2.95
Preskimmianine	7.14	SER315	3.09	3.69
4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl	5.92	GLY261 ASN263 GLN352 GLN356	1.94 2.29 2.76 2.57	2.89 3.25 3.55 3.30
Quercetin-3-o-xyloside	7.55	NI▪▪	-	-
Quercitrin	7.50	ARG308 ALA440 ASP442 GLY443 ALA444	3.30 1.78 and 2.23 3.18 2.52 2.45	3.83 2.75 and 3.13 3.60 3.39 3.23
Secologanin	8.07	ARG211 ARG343 GLU414 GLY415 GLY416	2.79 3.61 1.93 2.83 3.56	3.31 4.07 2.83 3.48 3.93
Tetradecanoic acid	6.92	ASN263	3.50	4.08
Orlistat	9.36	ARG211 SER313	2.54 3.22	3.04 4.02

Note: NI▪▪- No hydrogen bond interactions.

(hCN 2) enzyme (as shown in Table 3). However, three ligands (Alpha-amyrin, Atractylodin and Quercetin-3-o-xyloside) does not shown any interaction with the amino acid residue of human Carnosinase 2 (hCN 2) enzyme.

DISCUSSION

Sharp and coworkers (2007) had demonstrated that *Cissus quadrangularis* (Pirandai- stem and leaf extracts) shown to inhibit human lipase, porcine pancreatic amylase and *Saccharomyces cerevisiae* alpha glucosidase activities. Interestingly, Oben and colleagues (2015) had clinical demonstrated the effectiveness of using *C. quadrangularis* (CQR-300 and CORE) product in decreasing i) Body Weight (BW), ii) Body Fat (BF), iii) Total Cholesterol (T-CHO), iv) LDL-Cholesterol (LDL-C), v) Triglycerides (TG) and vi) fasting blood glucose (FBG) levels in humans. Similarly, Kuate and colleagues (2015) had clinical demonstrated the effectiveness of using *C. quadrangularis* (CQR-300) product in decreasing Body Weight (BW), along with enhancing blood parameters associated Metabolic Syndrome (MS) and obese in humans. Further, Lee and colleagues (2016) had demonstrated that *C. quadrangularis* (CQR-300 extracts) decrease Body Fat (BF) via by regulating the fatty acid biosynthesis in high fat diet induced obese mice. Furthermore, Lee and coworkers (2018) had reported that *C. quadrangularis* (CQR-300 extracts) suppress lipid accumulation via by down-regulating adipogenesis and lipogenesis in 3T3-L1 (mouse pre-adipocytes) cells.

Before performing docking, toxicity analysis was carried out in the present study, where no hepatotoxicity effect was predicted for thirty-two selected *C. quadrangularis* (Pirandai) ligands (as shown in Table 3). However, Orlistat (reference drug) has been predicated to have hepatotoxicity effect. This finding was on par with earlier report, where Orlistat showed fulminant hepatic failure (Sall *et al.*, 2014). Similarly, two ligands (3-O-Methylgallic acid and 9Z,12Z,15Z-Octadecatrienoic acid) of *C. quadrangularis* (Pirandai) were predicted to have Cytochrome P450 1A2 inhibitory activity. This result was in excellent correlation with previous reports, where gallic acid (parent compound of methyl gallic acid) and 9Z,12Z,15Z-Octadecatrienoic acid (from

Moringa oleifera) showed Cytochrome P450 1A2 inhibitory activity (Jumpa-Ngern, 2022; Parvathi *et al.*, 2022).

In the present docking analysis, eleven ligands of Pirandai and standard drug (Orlistat) have exhibited interaction with ASP 34 amino acid residue of Human Intestinal-type Fatty Acid Binding Protein (hI-FABP). This result was in excellent agreement with earlier report, where nitrazepam (lipophilic drug) showed interaction with ASP 34 amino acid residue of hI-FABP (Velkov *et al.*, 2005). Similarly, eleven ligands of Pirandai and standard drug (Orlistat) have shown interactions with SER 53 amino acid residue of human intestinal-type fatty acid binding protein (hI-FABP). This result was in excellent correlation with previous report, where nitrazepam (lipophilic drug) showed interaction with Ser 53 amino acid residue of hI-FABP (Velkov *et al.*, 2005). Further, eight ligands of Pirandai (Cosmosiin, 3,4-dimethoxyphenethyl alcohol, Gallocatechin gallate, Kaempferol-3-o-galactoside, Kaempferol-3-rutinoside, Quercetin-3-o-xyloside, Quercitrin and Secologanin) have exhibited interaction with TYR 14 amino acid residue of human Intestinal-type Fatty Acid Binding Protein (hI-FABP). This result was in excellent agreement with earlier report, where nitrazepam (lipophilic drug) showed interaction with TYR 14 amino acid residue of hI-FABP (Velkov *et al.*, 2005).

In the current docking analysis, four ligands of Pirandai (3,4-dimethoxyphenethyl alcohol, Kaempferol-3-rutinoside, 2-oxo-4-methylthiobutanoic acid and Secologanin) have exhibited interaction with ARG 343 amino acid residue of human Carnosinase 2 (hCN 2) enzyme. This result was in excellent agreement with earlier reports, where Bestatin (BES) and KKL-35 showed interaction with ARG 343 amino acid residue of hCN 2 (Toviwek *et al.*, 2024, Homma *et al.*, 2025). Similarly, three ligands of Pirandai and standard drug (Orlistat) have shown interactions with GLU 166 amino acid residue of human Carnosinase 2 (hCN 2) enzyme. This result was in excellent correlation with previous report, where Bestatin (BES) and KKL-35 showed interaction with GLU 166 amino acid residue of hCN 2 (Homma *et al.* 2025). Further, two ligands of Pirandai (Dyphylline and n-Hexadecanoic acid) have shown interactions with HIS 380 amino acid residue of human Carnosinase 2 (hCN 2) enzyme. This result was in excellent agreement with earlier report, where Bestatin (BES) and KKL-35 showed interaction with HIS 380 amino acid residue of hCN 2 (Homma *et al.*, 2025).

The present finding is only based on *in silico* (molecular docking) method which gives new understanding about the 32 chosen *C. quadrangularis* (Pirandai) ligands and their interactions with 2 selected target proteins. However, further *in vitro* [8-anilino-1-naphthalene sulfonate (ANS) binding assay] and *in vivo* studies are required to confirm 32 chosen ligands as modulating agents of two human proteins (hI-FABP and hCN 2).

CONCLUSION

In the current study, the thirty-two chosen *Cissus quadrangularis* (Pirandai) phytochemicals have shown the potential to dock with two target human proteins (hI-FABP and hCN 2). Moreover, two ligands of Pirandai (Alpha-amyrin, Atractylodin) do not exhibit any interaction with amino acid residues of both hI-FABP and hCN 2 respectively. Thus, the current finding give new knowledge about the thirty-two selected phytochemicals of *C. quadrangularis* (Pirandai) as potent modulating agents of hI-FABP and hCN 2, which will aid in managing good health and well-being especially obesity related disorders.

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ABBREVIATIONS

hI-FABP: Human intestinal-type fatty acid binding protein; **hCN 2:** Human carnosinase 2; **CID:** Compound Identifier; **2D:** Two dimensional; **3D:** Three dimensional; UniProt: Universal Protein Resource; **PDB:** Protein Data Bank; **HBE:** Highest binding energy; **MBE:** Maximum binding energy; **LBE:** Least binding energy; **PLIP:** Protein-Ligand Interaction Profiler; **RMSD:** Root mean square deviation; **BW:** body weight; **BF:** body fat; **T-CHO:** total cholesterol; **LDL-C:** LDL-cholesterol; **TG:** Triglycerides; **FBG:** Fasting blood glucose; **MS:** Metabolic syndrome; **ANS:** 8-anilino-1-naphthalene sulfonate.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, B,T., R.N.; methodology, B.T., R.N.; software, B.T., R.N.; formal analysis, B.T., B.D., S.B.S., R.N.; investigation, B.T., B.D., S.B.S., R.N.; resources, B.T., R.N.; data curation, B.T., B.D., S.B.S., R.N.; visualization, B.T., B.D., S.B.S., R.N.; supervision, R.N.; project administration, B.T., R.N.; writing-original draft preparation, B.T., B.D., S.B.S., R.N.; writing-review and editing, B.T., B.D., S.B.S., R.N.; All authors have read and agreed to the published version of the manuscript.

SUMMARY

In the present study, thirty-two selected constituents of *Cissus quadrangularis* (Pirandai) were studied on the docking behaviour of human intestinal-type Fatty Acid Binding Protein (hI-FABP) and human Carnosinase 2 (hCN 2) by utilizing the Swiss dock method. The molecular docking analysis showed that Ligustrosidic acid and Linarin of *C. quadrangularis* (Pirandai)

have exhibited the highest binding energy (-9.50 and -10.01 kcal/mol) with the hI-FABP and hCN 2 respectively.

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