RESEARCH ARTICLE

Molecular Docking Guided Screening of Phytoconstituents from *Artemisia iwayomogi* as Potential Peroxisome Proliferator-activated Receptor (PPAR) δ Agonists

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ABSTRACT

Metabolic syndrome is a disease condition characterized by decreased insulin sensitivity, hyperlipidemia, abdominal obesity, hypertension, and myocardial diseases, primarily related to a high-fat diet and lack of physical exercise. Peroxisome proliferator-activated receptor (PPAR) δ stimulation changes the body's energy fuel preference to fats from sugar. PPARδ is expressed universally in all tissues of the human body, particularly those involving lipid metabolism. PPARδ is an evolving pharmacological target for the pharmacotherapeutics of diseases linked to metabolic syndrome. *Artemisia iwayomogi* ethanol extract was reported as PPARδ agonist and reduced diet-induced overweight via stimulation of fatty acid oxidation in the skeletal muscles. The present study is designed to evaluate *in silico* some phytoconstituents, including 4 coumarins, 12 flavonoids, 5 phenolic compounds and 7 caffeoyl-quinic acid derivatives found in *A. iwayomogi* to explore their binding mode and interactions with the PPARδ protein. A total of 28 compounds evaluated *in silico*, 16 compounds displayed good binding free energy, and significant docking interactions with the binding site residues of PPARδ protein supporting the *in vitro* PPARδ agonistic activity of *A. iwayomogi* extract. Amongst these, scopolin, patuletin, patuletin-3-glucoside, 1,2-bis(4-hydroxy-3-methoxyphenyl)prop-1,3-diol, 3-caffeoylquinic acid, and 1,3-dicaffeoylquinic acid displayed most significant binding interactions with binding site residues of PPARδ. This information can be utilized for developing potent and non-toxic natural PPARδ agonists for the management of disorders related to metabolic syndrome.

Keywords: *Artemisia iwayomogi*, Metabolic syndrome, Phytoconstituents, PPARδ, PPARδ agonists.

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INTRODUCTION

Metabolic syndrome (MS) is a disease condition characterized by numerous related clinical conditions such as central obesity, reduced insulin sensitivity, hypertension, hyperlipidemia, and cardiovascular diseases, and is progressively prevailing in the industrialized nations globally.[1-2] Peroxisome proliferator-activated receptors (PPARs) control expression of the genes responsible for controlling the breakdown of carbohydrates, fatty acids and cholesterol, and cell proliferation. PPARδ (NR1C2) possesses 441 amino acid residues and is expressed universally in each tissue of the human body, usually at higher levels compared to PPARα and PPARγ, but it is the least-studied PPAR. Though, it is predominantly abundant in the body tissues linked to the catabolism of lipids such as kidney, hepatic system, intestine, adipose tissue, and brain. It controls β-oxidation of the fatty acids, primarily in the skeletal muscles and muscles of the cardiac system, and controls concentrations of glucose and cholesterol in blood.[3-7] Investigations conducted on animals indicate that the stimulation of PPARδ outcomes in numerous favorable pharmacological effects such as decreased weight-gain, augmented lipid metabolism in the skeletal muscles and cardiovascular function, as well as suppressed atherogenic inflammation. PPARδ controls the expression of various enzymes that are linked to glucose metabolism and β-oxidation of fatty acids via direct regulation of transcription and repression of the inflammatory reactions in the macrophage cells. These therapeutically valuable actions of PPARδ stimulation are a result of the ability of PPARδ to control production and breakdown of energy, diminished fat problem, and defense against lipo-toxicity triggered due to the buildup of lipids. The actions of PPARδ agonists are analogous to the circumstances due to physical exercise, fasting, and cold exposure. Thus, PPARδ represents an emergent pharmacotherapeutic target for the management of MS and the development of selective PPARδ agonists might be advantageous in the therapeutics of MS.[8-12] The results from the ligand-binding assays recommend that diverse types of lipid-based derivatives, including saturated fatty acids, polyunsaturated fatty acids, and eicosanoids (like prostaglandin A1 and carboprostacyclin) interacts with

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PPARδ.[13-14] In addition to these natural endogenous agonists of PPARδ, a great number of selective synthetic organic molecules of diverse chemical nature were developed in past two decades which were more strong agonists of PPARδ compared to the natural endogenous agonists having pharmacologically useful roles in disturbed metabolism of lipids, central obesity and reduced sensitivity of insulin.[15-18] Efforts are going on even now to design newer, selective, and strong agonists of PPARδ with better safety profile for the management of MS and some had advanced in the clinical trials. However, no PPARδ agonist is available/approved clinically for human use. Upcoming usage of safe, specific and highly effective PPARδ agonists in down-regulating major metabolic disorders could relieve some of the major health concerns worldwide.[19] Some plant-based compounds including 2,4-dimethyl-4-hydroxy-16-phenylhexadecanoic acid 1,4-lactone,[20] 4′-geranyloxyferulic acid,[21] 3',5'-dimethoxy-7-hydroxyisoflavone,[22] ombuin-3-O-β-D-glucopyranoside,[23] panduratin A[24] and bavachinin[25] were reported as potent and selective PPARδ agonists.

Recently, ethanolic extract of *Artemisia iwayomogi* was reported to activate PPARδ, resulting in the stimulation of fatty acid oxidation in the skeletal muscles. *A. iwayomogi* is locally called as 'haninjin' or 'dowijigi', a habitual herb mostly abundant in Korea and belongs to the family Compositae.[26] *A. iwayomogi* has been utilized for vegetables and meals including tea, rice cake, and soup and also used for the therapeutics of numerous disease conditions such as hepatitis, inflammation, metabolic syndrome and immune-related illnesses (for liver protection), anticancer, antibacterial, antifungal and as a diuretic.[26-28] Various types of phytoconstituents were reported in *A. iwayomogi* including coumarins, flavonoids, phenolic compounds, terpenoids (monoterpenes, diterpenes, and triterpenoids) and caffeoylquinic acid derivatives.[29-34]

In the current investigation, a total of 28 phytoconstituents of *A. iwayomogi* including 4 coumarin derivatives, 12 flavonoids, 5 phenolic compounds and 7 caffeoylquinic acid analogs were selected for the *in-silico* evaluation using docking studies in order to explore their binding mode and interactions with the PPARδ protein (Figure 1).

MATERIAL AND METHODS

Prediction of pharmacokinetic parameters

All the phytoconstituents selected for the *in silico* molecular docking studies were evaluated for the prediction of pharmacokinetic parameters associated to absorption, distribution, metabolism, and excretion (ADME) by employing FAF-Drugs4 ('Free ADME-Tox Filtering' tool); and accessed for drug-likeness using Lipinski's rule.[35-36]

In silico prediction of toxicity

All the phytoconstituents were evaluated for the prediction of possible toxicity and safety of these compounds using "pkCMS" online server tool (a machine learning platform to predict the pharmacokinetic characteristics of small molecules which utilize graph-based signatures for development of predictive models).[37-38]

Molecular docking studies

Molecular docking investigations were performed for the selected phytoconstituents in the ligand-binding site of PPARδ employing AutoDock Vina[39] and AutoDock Tools 1.5.6 (ADT).[40] The 2D chemical structures ("SDF" format) of the ligands (selected phytoconstituents) were downloaded from the "PubChem" database[41] or sketched using MarvinSketch (Marvin, Version 18.5.0, 2018, ChemAxon Ltd., Budapest, Hungary) followed by conversion to 3D ("MOL2" format) using "Frog2" server.[42] The ligands ("MOL2" format) were converted to "PDBQT" files using ADT. After assessing a number of co-crystallized structures for PPARδ available in the protein data bank, the best ligand-bound complex was selected (PDB entry: 2Q5G) based on higher resolution and key binding interactions between the PPARδ and small molecule agonists. The "PDB" file of PPARδ protein was edited using PyMOL (The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.) by removing the A-chain of protein, co-crystallized agonist, all the water molecules along with other non-interacting species. The "PDBQT" file of PPARδ protein was generated from "PDB" file using ADT.[43-44] The "Grid" tool of ADT was used to calculate the grid parameters and all the information concerning input files (PPARδ protein and ligands), grid box (grid size and geometry of the ligand-binding site of PPARδ) and out files (docked molecules and log files) were saved in "txt" file.[45-46] Docking was performed for all the ligands in the binding site of the PPARδ protein using the command line on Windows. The reference ligand (PDB entry: 2Q5G) was docked in the binding site of PPARδ and compared with that of the co-crystallized PPARδ agonist for determining the accuracy of the docking protocol. The 3-D optimized ligands were docked in the ligand-binding site of the refined PPARδ protein and scored by the scoring function. The binding free energy (ΔG, kcal/mol) for each compound was reported in a log file, and the binding interactions of the ligands in the ligand-binding site of the PPARδ protein were analyzed using PyMOL molecular graphics tool.[47-49]

RESULTS AND DISCUSSION

Prediction of ADME properties

The ADME properties such as molecular weight (MW), partition coefficient (log P), distribution coefficient (log D), water solubility (log S_w), topological polar surface area (tPSA), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), solubility (mg/L) and number of rotatable bonds (NRB) were calculated for all the phytoconstituents chosen for the docking studies. Almost all of the compounds showed good pharmacokinetic ADME parameters for oral bioavailability (Table 1) and drug-likeness as contrived by using "Lipinski's rule of five."

Prediction of toxicity and safety

The possible toxicity (mutagenicity, carcinogenicity, cardiotoxicity, hepato-toxicity and skin irritation) for all the phytoconstituents selected for the *in-silico* docking studies was

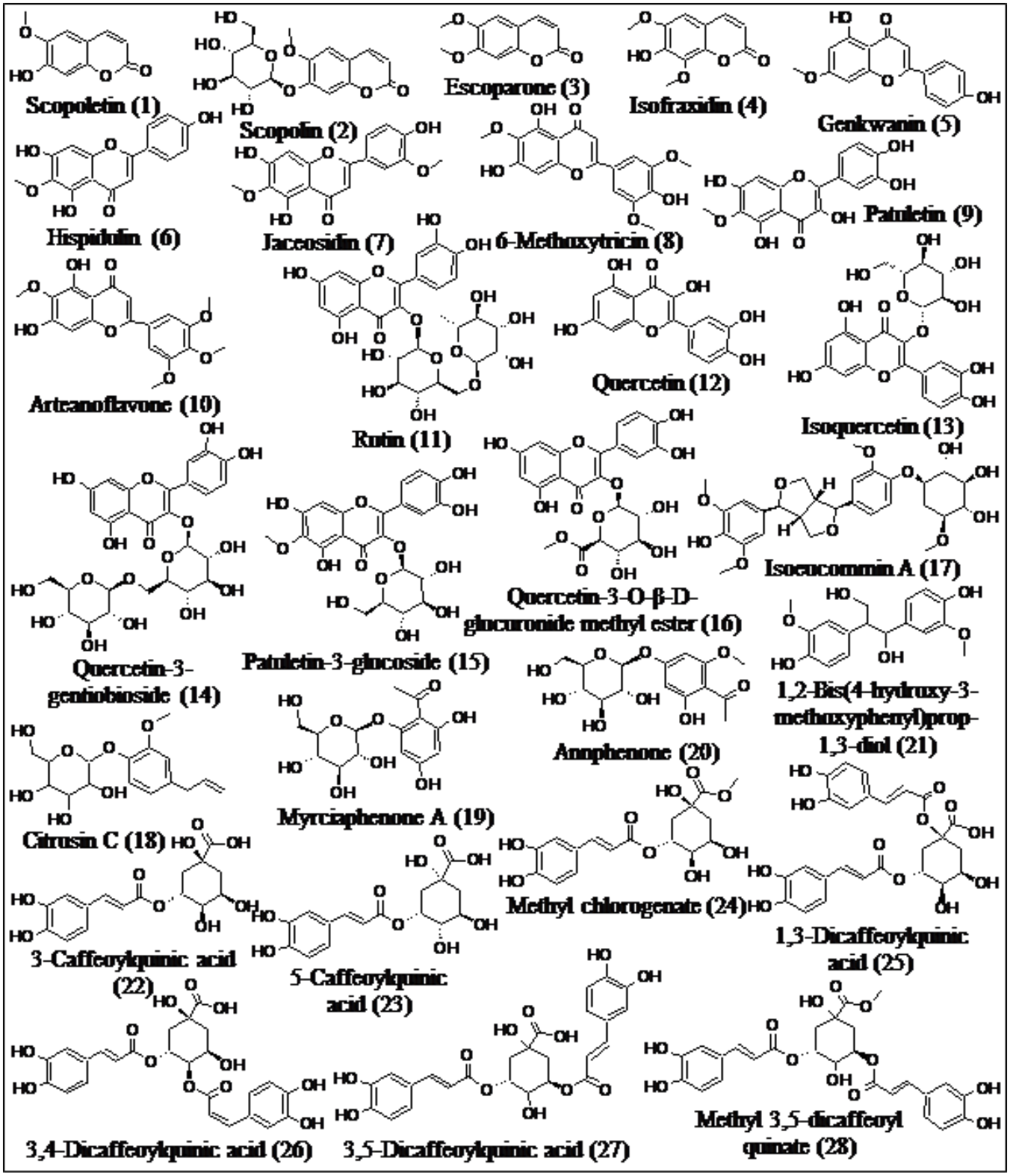

Figure 1: Phytoconstituents of *A. iwayomogi* selected for the *in-silico* molecular docking studies with the PPARδ protein.

Table 1: ADME properties predicted for the phytoconstituents selected for the *in-silico* docking studies.

Comp.	*MW*	*log P*	*log D*	*log Sw*	*tPSA*	*HBA*	*HBD*	*Solubility*	*NRB*
1	192.2	1.53	1.27	-2.27	59.6	4	1	19938.7	1
2	354.3	-1.05	-0.95	-1.28	138.8	9	4	98185.8	4
3	206.2	1.71	1.47	-2.36	48.7	4	0	19474.6	2
4	222.2	1.50	1.01	-2.32	68.9	5	1	21940.5	2
5	284.3	3.35	2.80	-3.94	79.9	5	2	5529.9	2
6	300.3	2.99	2.09	-3.80	99.8	6	3	6706.6	2
7	330.3	3.07	1.95	-3.94	109.0	7	3	6452.7	3
8	360.3	3.04	1.77	-4.01	118.3	8	3	6552.9	4
9	332.3	2.14	1.22	-3.45	140.3	8	5	10599.5	2
10	374.3	3.37	1.94	-4.22	107.3	8	2	5518.1	5
11	610.5	-1.29	-1.88	-2.58	269.1	16	10	46321.5	6
12	302.2	1.54	1.01	-2.99	131.0	7	5	15228.1	1
13	464.4	0.36	-1.16	-2.91	210.2	12	8	25415.6	4
14	626.5	-1.78	-2.93	-2.30	289.3	17	11	62750.7	7
15	494.4	0.33	-0.90	-2.99	219.4	13	8	24839.5	5
16	492.4	0.93	-0.69	-3.36	216.2	13	7	17035.4	5
17	550.5	0.45	-0.15	-3.13	165.8	12	5	24055.3	8
18	326.3	0.03	0.34	-1.58	108.6	7	4	66890.6	6
19	330.4	-0.97	1.11	-1.12	156.9	9	6	107661.2	4
20	344.3	-0.64	-0.85	-1.34	145.9	9	5	89936.0	5
21	320.3	1.37	1.32	-2.50	99.4	6	4	26302.7	6
22	354.3	-0.42	-3.69	-1.55	167.6	9	6	75550.3	5
23	354.3	-0.42	-3.69	-1.55	167.6	9	6	75550.3	5
24	368.3	-0.10	-0.13	-1.76	153.7	9	5	63294.2	6
25	516.4	1.52	-1.30	-3.55	214.1	12	7	14817.5	9
26	516.4	1.52	-1.28	-3.55	214.1	12	7	14817.5	9
27	516.4	1.52	-1.29	-3.55	214.1	12	7	14817.5	9
28	530.5	1.85	2.29	-3.77	200.3	12	6	12189.4	10

accessed using "pkCSM" online server tool which depend on the "graph-based signatures". As per the results depicted in Table 2; all the selected phytoconstituents displayed little or no toxicity possibility.

In silico docking studies

In silico molecular docking, investigations were performed to explore the affinity and binding interactions of these phytoconstituents using AutoDock Vina in the ligand-binding site of PPARδ. The reference PPARδ agonist produced an analogs binding pattern and overlay on the binding mode of co-crystallized PPARδ agonist (PDB entry: 2Q5G) with ΔG of -9.1 kcal/mol validating accuracy of the docking procedure. Amongst the selected phytoconstituents evaluated in silico, compounds 1–5, 7–10, 15, 19–22, 25, and 26 demonstrated considerable binding in the ligand-binding site of PPARδ as determined by analyzing their bonding in terms of H-bond and hydrophobic interactions and binding free energy (Table 3). For the rest of the molecules, the docking algorithm produced a different binding pattern, and molecules were randomly oriented in the binding site.

Based on the lowest binding free energy (ΔG) and docking interactions in the binding site of the PPARδ, compounds 2, 9, 15, 21, 22 and 25 were further investigated in minutiae using PyMOL for exploring binding interactions of these compounds with the ligand-binding site residues of PPARδ. Super-imposing of the docked poses of scopolin (2), patuletin (9), patuletin-3-glucoside (15), 1,2-bis(4-hydroxy-3-methoxyphenyl)prop-1,3-diol (21), 3-caffeoylquinic acid (22) and 1,3-dicaffeoylquinic acid (25) with that of the co-crystallized PPARδ agonist, {7-[2-(3-morpholin-4-yl-prop-1-ynyl)-6-(4-trifluoromethyl-phenylethynyl)-pyridin-4-ylsulfanyl]-indan-4-yloxy}-acetic acid (PDB entry: 2Q5G) in the ligand-binding site of PPARδ demonstrated that the selected molecules had the similar binding and orientation pattern in the ligand-binding site of PPARδ as that of the co-crystallized PPARδ agonist (Figure 2).

The docked pose (Figure 3) of scopolin (2) showed H-bond interactions between 'OH' group and 'NH' of Gln286, Lys367 and His449 residues with bond length of 3.0, 4.2 and 3.1 Å, respectively and the flavone moiety protruded in the hydrophobic pocket showing interactions with Cys285, Leu330 and Ile333 residues in the ligand-binding site of

Table 2: Toxicity prediction for the selected phytoconstituents obtained using "pkCSM" online server.

Comp.	*Muta-genicity*[a]	*Cardio-toxicity*[b]	*Acute toxicity*[c]	*Chronic toxicity*[d]	*Max. tolerated dose*[e]	*Hepato-toxicity*	*Skin irritation*
1	No	No	1.950	1.378	0.614	No	No
2	No	No	2.391	3.756	0.393	No	No
3	No	No	2.345	2.408	0.494	No	No
4	No	No	2.326	1.825	0.560	No	No
5	No	No	2.238	1.790	0.032	No	No
6	No	No	2.402	1.634	0.279	No	No
7	No	No	2.333	2.648	0.502	No	No
8	No	No	2.207	1.982	0.247	No	No
9	No	No	2.508	2.677	0.570	No	No
10	No	No	2.311	1.968	0.287	No	No
11	No	No	2.491	3.673	0.452	No	No
12	No	No	2.471	2.612	0.499	No	No
13	No	No	2.541	4.417	0.569	No	No
14	No	No	2.483	4.945	0.480	No	No
15	No	No	2.612	3.848	0.525	No	No
16	Yes	No	2.673	3.818	0.551	No	No
17	No	No	2.763	3.930	0.266	No	No
18	No	No	1.950	3.462	0.860	No	No
19	No	No	2.083	4.102	0.878	No	No
20	No	No	2.869	3.755	0.901	Yes	No
21	No	No	2.132	2.521	0.464	No	No
22	No	No	1.973	2.982	0.134	No	No
23	No	No	2.188	3.763	0.694	No	No
24	No	No	1.844	2.403	0.312	No	No
25	No	No	2.567	3.459	0.367	No	No
26	No	No	2.626	4.131	0.393	No	No
27	No	No	2.496	3.890	0.422	No	No
28	No	No	2.475	3.568	0.435	No	No

[a]Mutagenicity was accessed using AMES test; [b]Cardiotoxicity was accessed using hERG-I and hERG-II inhibition; [c]Acute toxicity: Oral rat acute toxicity (*i.e.*, LD_{50} in mol/kg); [d]Chronic toxicity: Oral rat chronic toxicity (log mg/kg_bw/day); [e]Max. tolerated dose (Human): log mg/kg/day.

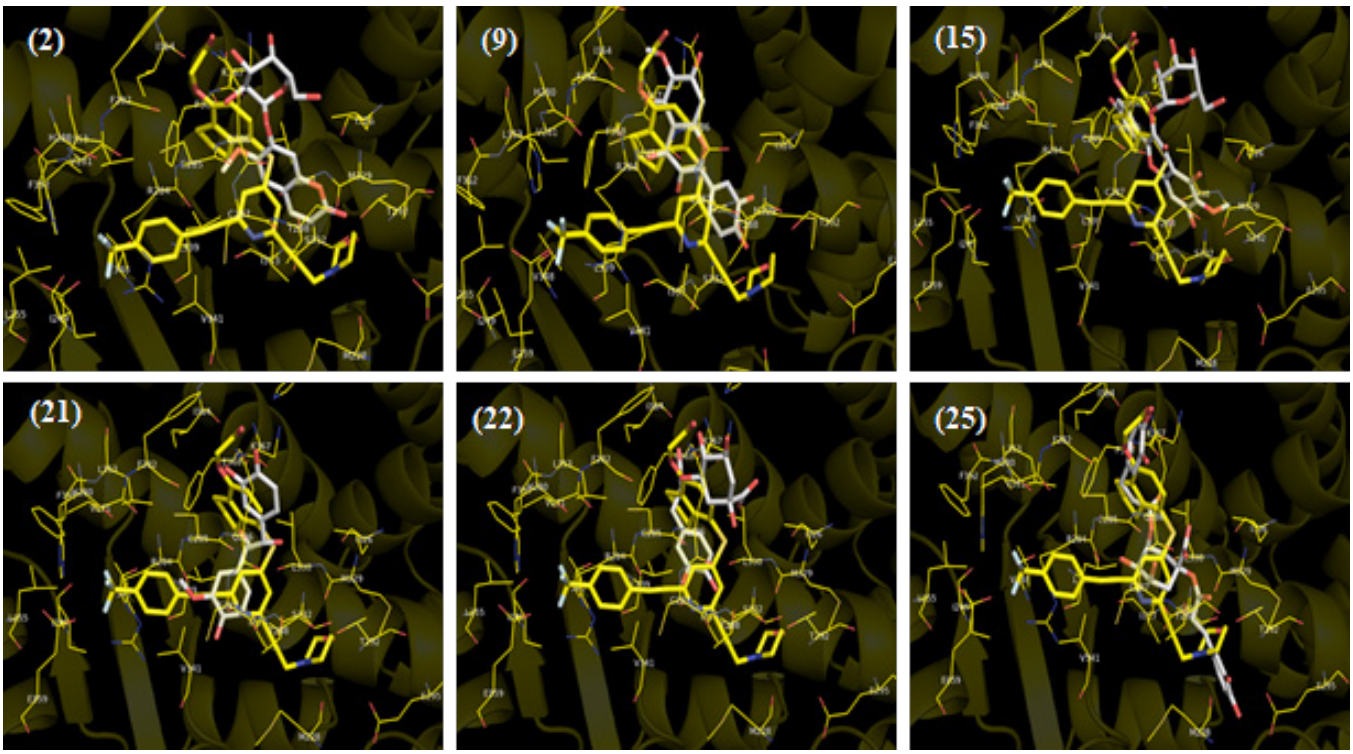

Figure 2: Super-positioning of the best-docked poses of scopolin (2), patuletin (9), patuletin-3-glucoside (15), 1,2-bis(4-hydroxy-3-methoxyphenyl) prop-1,3-diol (21), 3-caffeoylquinic acid (22) and 1,3-dicaffeoylquinic acid (25) (white sticks) on that of the co-crystallized PPARδ agonist (PDB entry: 2Q5G) (yellow sticks) in the ligand-binding site of the PPARδ protein.

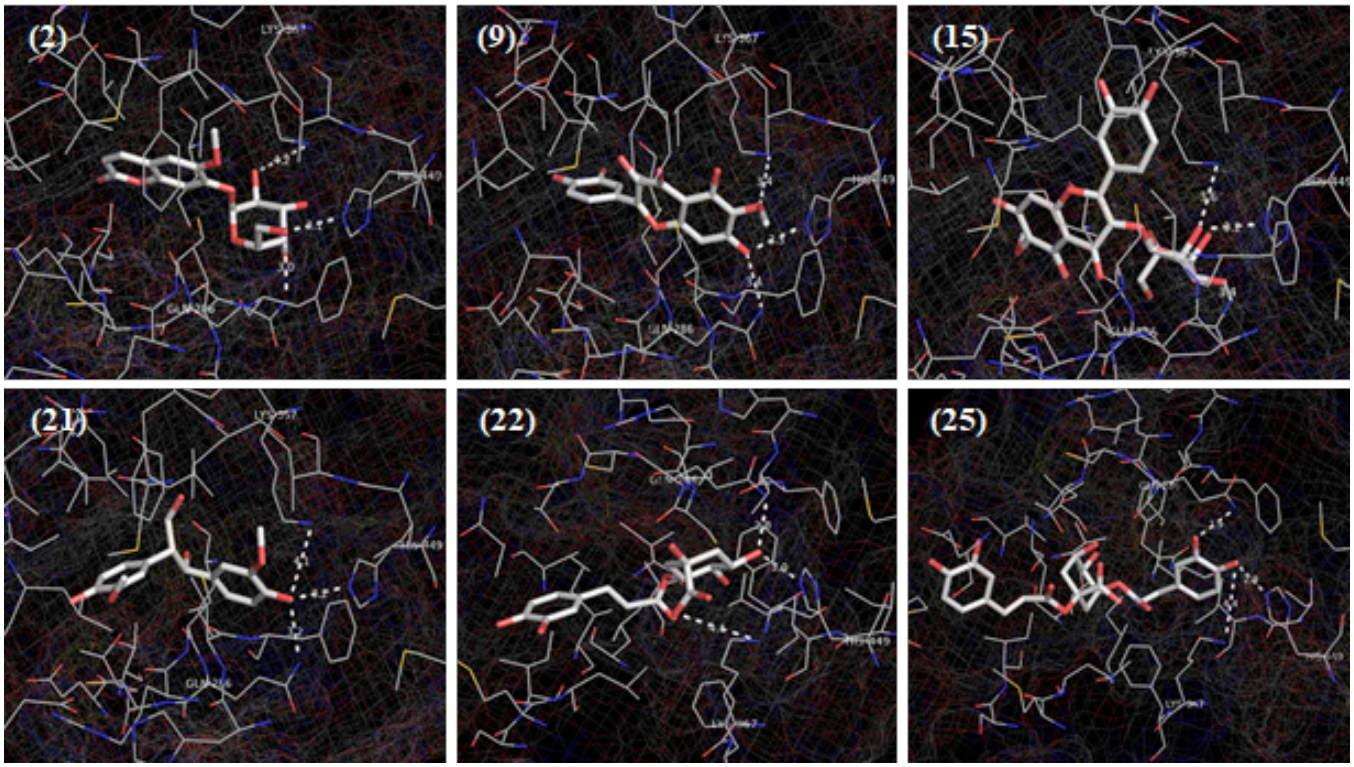

Figure 3: Best docked poses of scopolin (2), patuletin (9), patuletin-3-glucoside (15), 1,2-bis(4-hydroxy-3-methoxyphenyl)prop-1,3-diol (21), 3-caffeoylquinic acid (22) and 1,3-dicaffeoylquinic acid (25) showing H-bond interactions with the ligand-binding site residues of the PPARδ protein.

Table 3: Docking score (ΔG) and binding interactions of the selected phytoconstituents with the PPARδ protein.

Comp.	*ΔG*	*Residues involved in H-bond interactions (distance (Å))*	*Residues involved in the hydrophobic interactions*
1	-6.0	Lys367 (4.6)	Leu330
2	-7.5	Gln286 (3.0), Lys367 (4.2), His449 (3.1)	Cys285, Leu330, Ile333
3	-5.9	Gln286 (3.2), His449 (4.3)	Leu330, Ile333, Leu339, Ile363
4	-7.4	Gln286 (3.1), Lys367 (4.3), His449 (3.0)	Leu330, Ile333, Leu339
5	-7.7	Gln286 (3.3), Lys367 (4.9), His449 (3.4)	Leu330, Ile333, Leu339
6	-5.3	-	-
7	-6.9	Gln286 (4.6), His449 (4.6)	Leu330, Ile333, Leu339
8	-6.7	Lys367 (4.5)	Leu330
9	-7.5	Gln286 (3.4), Lys367 (3.4), His449 (3.3)	Cys285, Leu330, Ile333, Leu339, Ile363, Ile364
10	-5.4	Gln286 (3.4), His449 (4.5)	Leu330, Ile333, Leu339
11	-5.9	-	-
12	-5.8	-	-
13	-5.4	-	-
14	-6.4	-	-
15	-7.8	Gln286 (3.4), Lys367 (3.6), His449 (3.2)	Cys285, Ile326, Leu330, Ile333, Leu339, Ile364
16	-5.9	-	-
17	-5.8	-	-
18	-6.1	-	-
19	-7.6	Gln286 (4.8), Lys367 (3.8), His449 (4.5)	Cys285, Leu330, Ile333, Leu339
20	-6.7	Gln286 (3.0), His449 (4.0)	Met228, Leu330, Ile333, Ile363, Ile364
21	-7.3	Gln286 (3.2), Lys367 (4.1), His449 (3.2)	Leu330, Leu339, Val341, Ile364
22	-7.4	Gln286 (3.7), Lys367 (3.1), His449 (3.2)	Ile326, Met329, Leu330, Ile333
23	-6.2	-	-
24	-6.7	-	-
25	-8.1	Gln286 (2.9), Lys367 (4.1), His449 (2.8)	Phe226, Met228, Glu291, Leu330, Ile333, Ile363, Ile364
26	-6.8	Gln286 (3.8)	Leu330, Ile333
27	-5.5	-	-
28	-6.2	-	-
1FA*	-9.1	Gln286 (3.7), Lys367 (3.1), His449 (3.2)	Cys285, Leu330, Ile333, Ile363, Ile364

*1FA: Co-crystallized PPARδ agonist used as control (reference ligand) in the *in-silico* docking study.

PPARδ. Patuletin (9) showed H-bond interactions (between phenolic 'OH' and 'O', and 'NH' of Gln286, Lys367 and His449 residues with bond length of 3.4, 3.4 and 3.3 Å, respectively) with PPARδ. The 3,4-dihydroxyphenyl moiety of patuletin protruded in the hydrophobic pocket comprising of Leu330 and Ile333 residues and flavone moiety showed hydrophobic interactions with Cys285, Leu339, Ile364, Ile364, and Ile365 residues in the ligand binding site of PPARδ.

Patuletin-3-glucoside (15) showed H-bond interactions (between 'OH' and 'NH' of Gln286, Lys367 and His449 residues with a bond length of 3.4, 3.6 and 3.2 Å, respectively) with PPARδ. Flavone moiety of patuletin-3-glucoside showed hydrophobic interactions with Ile326, Leu330 and Ile333 residues; and 3,4-dihydroxyphenyl ring protruded in the hydrophobic cavity showing interactions with Cys285, Leu330, Leu339 and Ile364 residues in the ligand binding site of PPARδ. 1,2-Bis(4-hydroxy-3-methoxyphenyl)prop-1,3-diol (21) showed H-bond interactions (between phenolic 'OH' and 'O', and 'NH' of Gln286, Lys367 and His449 residues with bond length of 3.2, 4.1 and 3.2 Å, respectively) and hydrophobic interactions with Leu330, Leu339, Val341 and Ile364 residues in the ligand-binding site of PPARδ. 3-Caffeoylquinic acid (22) showed H-bond interactions (between phenolic 'OH' and 'NH' of Gln286, Lys367, and His449 residues with a bond length of 2.8, 4.1 and 3.0 Å, respectively) with PPARδ. Caffeoyl moiety of 3-caffeoylquinic acid protruded in the hydrophobic pocket containing Ile326, Met329, Leu330, and Ile333 residues in the ligand-binding site of PPARδ. 1,3-Dicaffeoylquinic acid (25) showed H-bond interactions (between phenolic 'OH' and 'NH' of Gln286, Lys367, and His449 residues with a bond length of 2.9, 4.4 and 2.8 Å, respectively) with PPARδ. 1,3-Dicaffeoylquinic acid showed H-bond interactions with Phe226, Met228, Glu291, Leu330, Ile333, Ile363, and Ile364 residues in the ligand-binding site of PPARδ (Figure 3).

The best-docked poses of the selected phytoconstituents and overlay with the PDB ligand of 2Q5G (standard PPARδ agonist) could help in predicting that compounds obtained from *A. iwayomogi* may possibly act as strong PPARδ agonists supporting the *in vitro* PPARδ agonistic activity of the ethanolic (95%) extract of aerial parts of *A. iwayomogi* reported by Cho et al., (2012)[26].

In summary, 28 phytoconstituents of *A. iwayomogi* were evaluated *in silico* using molecular docking studies for exploring binding interactions of these compounds with the binding site residues of PPARδ. Amongst these phytoconstituents, scopolin, patuletin, patuletin-3-glucoside, 1,2-bis(4-hydroxy-3-methoxyphenyl)prop-1,3-diol, 3-caffeoylquinic acid and 1,3-dicaffeoylquinic acid displayed most significant binding interactions with binding site residues of PPARδ supporting the *in vitro* PPARδ agonistic activity of *A. iwayomogi* reported earlier. Almost all the selected compounds showed good pharmacokinetic properties for oral availability (or drug-likeness) and presented a low toxicity profile (predicted using FAF-Drugs4 server and pkCSM online tool, respectively). Structural modifications and further studies on these phytoconstituents could be done to develop safe and potent PPARδ agonists for the treatment of disorders related to metabolic syndrome.

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