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IN-SILICO ANALYSIS OF SECONDARY METABOLITES THAT INHIBIT ALDOSE REDUCTASE TARGETING DIABETIC RETINOPATHY

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Table S1: Interaction of secondary metabolites with protein 4JIR

Metabolites	Binding Affinity (kcal/mol)	Amino acid Residues	Interaction Type	Interaction Distance Å
Apigenin	-8.7	TRP 20, TRP 111, VAL 47, NAP 404	Hydrogen bond, Pi-Sigma	4.65, 2.15, 3.92, 2.19
Afzelin	-8. 5	TYR 48, TRP 20, TRP 111, NAP 404, VAL 47, TYR 48	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.44, 2.56, 2.11, 2.18, 4.99, 4.72, 5.59
Aurantio-obtusin	-8.4	VAL 47, TRP 20, TYR 48, LEU 300, TRP 219, NAP 404	Pi-Alkyl, Hydrogen bond, Pi-Pi stacked	3.86, 5.04, 4.87, 2.36, 4.73, 4.14, 3.08
Allocryptopine	-8.2	LEU 301, ALA 299, LEU 300, CYs 298	Hydrogen bond, Pi-Sulfur, Pi-AlKyl	1.67, 3.08, 5.17, 5.59
Astragallin	-8.0	HIS 110, ALA 299, LEU 301, TRP 219, TRP 20, NAP 404, CYS 298	Hydrogen bond, Pi-Pi stacked, Pi-Pi T-shaped, Pi-Sulfur	1.84, 2.37, 5.97, 4.70, 6.26, 5.29, 5.75, 4.90
Beta-glucogallin	-7.1	HIS 110, NAP 404, ALA 299, VAL 297, LEU 301, TRP 219, LEU 300	Hydrogen bond, Pi-Pi stacked, Pi-alkyl	2.46, 2.66, 1.80, 2.19, 5.24, 5.57, 3.63
Brazilin	-7.6	TRP 111, NAP 404, TRP 20, VAL 47, TRP 79	Hydrogen bond, Pi-Pi T-shaped, Pi-alkyl	2.22, 2.76,2.74, 3,24, 5.14
Butein	-8.2	HIS 110, TRP 111, TRP 219, ALA 299, LEU 301	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi stacked, Pi-Pi T-shaped	2.42, 5.44, 4.91, 5.48, 4.74
Capillarisin	-7.3	HIS 110, SER 302, CYS 298, PHE 122, LEU 124	Hydrogen bond, Pi-Pi stacked, Alkyl, Pi-Sulfur	2.22, 2.48, 4.89, 3.71, 4.52, 2.48
Cinnamaldehyde	-5.7	TYR 48, HIS 110, TRP 20, CYS 298	Hydrogen bond, Pi-sigma, Pi-Pi stacked, Pi-Alkyl	2.34, 2.24, 3.77, 5.96, 4.80
Cistanoside F	-6.7	HIS 110, SER 302, PHE 122, VAL 47	Hydrogen bond, Pi-Pi T-shaped, Carbon-Hydrogen bond	2.90, 2.09, 5.42, 3.33
Cuminaldehyde	-6.2	HIS 110, TYR 48, TRP 111, CYS 298, LEU 300, PHE 122	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.21, 2.30, 5.16, 4.86, 4.78, 4.93
Curcumin	-7.9	HIS 110, TYR 48, VAL 47, TRP 20, LEU 300, LEU 301, TRP 219	Hydrogen bond, Pi-Sigma, Alkyl, Pi-Alkyl	2.41, 2.69, 3.85, 4.62, 5.11, 4.30, 4.76
Caffeic acid	-6.4	HIS 110, TYR 48, TRP 111	Hydrogen bond,	2.56, 3.03, 1.60
Daidzein	-8.3	TRP 111, CYS 298, LEU 301, TRP 219, ALA 299, LEU 300	Hydrogen bond, Pi-Alkyl, Pi-Sigma, Pi-Pi stacked	2.69, 505, 3.99, 6.37, 4.26, 2.05, 2.46, 3.95

Decursidin	-9.2	HIS 110, TRP 111, PHE 122, TRP 219, ALA 299, LEU 301	Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.41, 1.98, 5.23, 3.73, 3.98, 4.89, 4.03, 4.25
Desmanthin -I	-8.5	TYR 48, LYS 21, TRP 20, NAP 404, TRP 111, TRP 219, PRO 218, VAL 47, PHE 122, PHE 121	Hydrogen bond, Carbon-Hydrogen, Pi-Sigma, Pi-Alkyl, Alkyl	2.29, 2.36, 2.21, 2.38, 2.12, 2.20, 5.22, 4.19, 3.94, 5.70, 5.40
Davidigenin	-7.9	HIS 110, TRP 20, CYS 298, NAP 404, LEU 301, ALA 299, TRP 219	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.07, 6.56, 4.88, 5.50, 4.76, 5.45, 2.19, 2.72
Davallialactone	-9.2	TYR 48, SER 22, TRP 20, TRP11, CYS 298, PHE 122, PRO 24	Hydrogen bond, Carbon-Hydrogen bond,Pi-Sulphur, Pi-Pi T-shaped, Pi-Alkyl,	2.43, 2.89, 2.11, 2.02, 1.92, 5.61, 4.97, 4.31, 3.04
Dehydroglyasperin D	-8.4	TYR 48, ALA 299, LEU 300, TRP 20, TRP 219, LEU 301, PHE 122, LEU 124, NAP 404, CYS 298	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl, Alkyl Pi-Pi stacked	2.07, 3.08, 2.30, 6.39,4.71, 4.19, 4.28, 3.95, 5.16, 4.73,
Desmethylanhydroicaritin	-8.4	PHE 122, TRP 20, TRP 79, VAL 47, TRP 111, TRP 219, CYS 298	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	4.89, 2.96, 5.27, 2.70, 1.87, 4.67, 4.14
Emodin	-8.2	HIS 110, TRP 20, CYS 298, LEU 301	Hydrogen bond, Pi-Alkyl, Alkyl Pi-Pi stacked	2.15, 2.77, 5.80, 5.35, 5.40, 4.56
Ellagic acid	-8.3	HIS 110, LEU 300, TRP 20, CYS 298	Hydrogen bond, Pi-Pi stacked, Pi-Alkyl	2.34, 1.99, 2.59, 6.55, 5.38, 5.98, 5.14, 4.52
Epiberberin	-8.9	TRP 20, SER 302, VAL 47, TRP111, CYS 298, HIS 110, TYR 48, PHE 122, NAP 404	Hydrogen bond, Carbon-hydrogen, Pi-Pi stacked, Alkyl, Pi-Alkyl	2.77, 4.78, 7.29, 2.90, 5.35, 5.01, 4.23, 5.20, 4.97, 3.58
Ergosterol Peroxide	-8.1	HIS 110, TRP 219, TRP 111, LEU 301, ALA 299, CYS 298, NAP 404	Hydrogen bond, Pi-Hydrogen bond donor, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	2.42, 6.29, 5.38, 2.90, 5.48, 4.76, 5.44
Eriodictyol	-8.8	HIS 110, LEU 301, SER 302, ALA 299, TRP 111, CYS 298, NAP 404, LEU 300	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.06, 2.17, 2.52, 2.29, 5.51, 4.68, 5.27, 5.45
Flaviolin	-6.2	HIS 110, TYR 48, TRP 20, VAL 47, CYS 298	Hydrogen bond, Pi-Pi stacked, Pi-Alkyl	2.58, 2.88, 5.565, 5.98, 4.83, 5.18
Galloyl Paeoniflorin	-9.3	HIS 110, TRP 111, ARG 296, ALA 299, LEU 301, TRP 219, TRP 20	Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	3.00, 2.16, 2.39, 2.65, 5.27, 3.56, 4.08, 4.42
Groenlandicine	-8.6	HIS 110, VAL 297, TRP 111, TRP 20, TRP 219, VAL 47, TRP 79, LEU 301, ALA 299, CYS 298	Hydrogen bond, Carbon -Hydrogen bond, Pi-Sulfur, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl, Alkyl	2.73, 3.27, 5.34, 6.88, 4.83, 4.99, 5.60, 4.35, 5.15, 3.91, 5.16, 4.85, 4.74
Ganoderic acid DF	-7.7	HIS 110, TRP 20	Hydrogen bond	2.73, 2.76
Genistein	-8.3	TRP 219, LEU 301, LEU 300, ALA 299, CYS 298	Pi-Pi stacked, Hydrogen bond, Pi-Alkyl,	4.46, 5.65, 2.79, 2.36, 2.81, 5.40
Ganomycin B	-8.1	HIS 110, TRP 111, TRP 219, LEU 301, CYS 298, VAL 47	Hydrogen bond, Pi-Sigma, Pi-Alkyl, Alkyl	2.54, 2.09, 5.13, 3.78, 4.13, 5.09, 4.98, 3.84, 5.38, 3.78, 4.13, 3.73, 4.79

Gallic acid	-5.8	TYR 48, TRP 111, VAL 47, HIS 220	Hydrogen bond, Pi-cation Pi-Pi T-shaped, Pi-Alkyl,	2.46, 2.35, 2.09, 4.70, 4.59
Gossypol	-8.5	HIS 110, TRP 20, CYS 298	Hydrogen bond, Pi-Pi stacked, Pi-Alkyl	2.86, 2.52, 6.76, 5.34, 4.97
Hypholomine B	-10.8	PHE 122, TRP 111, NAP 404, ALA 299, LEU 301, SER 302, LEU 124, CYS 298, TRP 219	Hydrogen bond, Pi-Hydrogen bond donor, Pi-Pi-Sigma, Pi-Pi stacked, Pi-Alkyl	1.95, 3.98, 2.04, 3.02, 1.69, 2.97, 5.19, 2.57, 2.05, 3.64, 5.25, 5.62
Isoangustone A	-9.8	TRP 20, SER 302, ALA 299, ARG 296, TRP 295, LYS 221, TRP 219	Pi-Alkyl, Hydrogen bond, Pi-Sigma	5.64, 2.39, 2.13, 2.31, 3.63, 2.51, 4.10, 4.45
Isocampneoside II	-8.1	TRP 111, LEU 301, SER 302, TRP 20, ARG 296, ALA 299, VAL 297, TRP 219, CYS 298	Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	1.95, 5.45, 2.81, 3.62,1.92, 2.11, 2.12, 2.80, 2.22, 5.23, 2.47, 2.93, 4.11, 4.82
Isoquercitrin	-7.9	HIS 110, ALA 299, TRP 219, TRP 20, TRP 111, NAP 404, CYS 298	Hydrogen bond, Pi-Sulfur, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	1.95, 2.43, 5.96, 4.70, 5.29, 5.65, 6.20, 5.79, 4.94
Isovitexin	-7.8	HIS 110, LEU 300, ALA 299, LEU 301, SER 302, TRP 219, TRP 111, CYP 298	Hydrogen bond, Carbon- Hydrogen bond, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	2.09, 2.26, 2.24, 2.71, 3.01, 4.67, 4.39, 5.40, 5.36, 4.71
Isoliquiritigenin	-8.1	VAL 47, HIS 110, TRP 111, CYS 298, LEU 300	Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl	3.77, 2.80, 1.99, 4.99, 2.62, 4.77, 2.40, 5.35
Irigenin	-8.1	SER 302, CYS 298, HIS 110, VAL 47, TYR 48, TRP 20, TRP 219, LEU 301	Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl,	1.96, 4.31, 2.42, 3.48, 5.00, 4.40, 5.60, 6.18, 3.63, 4.43
Jateorrhizine	-7.6	HIS 110, TRP 11, VAL 47, TRP 20, TRP 79, TYR 48, NAP 404, PRO 24	Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.85, 5.04, 2.31, 3.98, 4.19, 5.11, 4.87, 3.91, 4.76
Kakkalide	-8.6	HIS 110, LEU 300, TRP 20, PHE 122, VAL 47,	Hydrogen bond, Carbon-Hydrogen bond, Pi-Sigma, Pi-Pi stacked, Pi-Alkyl,	2.49, 2.35, 2.55, 3.62, 4.57, 5.42
Kurarinol	-8.7	HIS 110, NAP 404, LEU 300, SER 302, TRP 219, PHE 122, LEU 301, VAL 297	Hydrogen bond, Carbon-Hydrogen bond, Pi-Sigma, Pi-Pi stacked, Pi-Pi T-shaped Pi-Alkyl,	2.53, 2.81, 2.06, 2.44, 3.67, 6.07, 5.27, 4.48, 3.68
Kurarinone	-8.9	HIS 110, LEU 300, ALA 299, TRP 20, TRP 219, NAP 404, PHE 122, CYS 298, LEU 301,	Hydrogen bond, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	1.94, 2.31, 2.21, 4.51, 4.48, 4.39, 5.41, 5.31, 4.52
Kushenol E	-8.4	HIS 110, LEU 300, ALA 299, TRP 20, TRP 219, NAP 404, CYS 298,	Hydrogen bond, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	1.80, 2.21, 2.14, 4.54, 5.94, 4.62, 4.59, 4.61, 5.17
Licochalcone A	-7.7	HIS 110, NAP 404, TRP 20, PRO 218, TRP 219, LEU 301, VAL 47	Hydrogen bond, Pi-Alkyl, Alkyl	2.22, 2.26, 2.38, 4.18, 4.17, 4.61, 5.47
Loganin	-6.8	TYR 48, TRP 20	Hydrogen bond	2.79, 1.86
Lucidin	-7.9	TYR 48, TRP 20, NAP 404, PHE 122, CYS 298	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi stacked, Pi-Alkyl	2.35, 2.80,5.15, 2.61, 2.37, 3.99, 4.88, 5.05

Luteolin	-8.9	HIS 110, TRP 111, CYS 298, LEU 300, ALA 299, LEU 301, NAP 404	Hydrogen bond, Pi-Sulfur, Pi-Alkyl, Pi-Pi T-shaped,	2.20, 5.41, 5.47, 5.27, 2.22, 1.16, 5.25
Lucidumol A	-9.1	TYR 48, LYS 21, ALA 299, TRP 219	Hydrogen bond, Pi-Sigma	2.22, 3.03, 2.46, 2.09, 3.72
Maesanin	-6.8	ALA 299, LEU 300, LEU 301, TRP 20, PHE 121, PHE 122, TRP 79, VAL 47, NAP 404, HIS 110, CYS 298, TRP 219	Hydrogen bond, Pi-Pi stacked, Pi-Alkyl, Alkyl	1.93, 2.68, 1.95, 5.32, 5.36, 4.51, 4.62, 4.98, 4.98, 4.58, 5.39, 3.85, 4.96, 4.79, 4.92, 5.57, 5.10
Methyl lucidenate F	-8.9	HIS 110, TYR 48, LEU 300, ALA 299	Hydrogen bond	2.22, 2.74, 2.28, 2.65
Myrciaphenone B	-7.7	TRP 111, SER 302, ARG 296, ALA 299, VAL 297, LEU 300, LEU 301, TRP 219	Hydrogen bond, Pi-Sigma, Pi-Pi stacked, Pi-Alkyl	2.70, 2.06, 3.06, 2.32, 5.34, 2.79, 2.53, 3.80, 4.00
Naringenin	-7.9	HIS 110, TYR 48, VAL 47, TRP 20, LEU 300	Hydrogen bond, Pi-Pi stacked, Pi-Alkyl	2.96, 2.87, 2.91, 4.93, 5.45, 5.14
Nodakenin	-8.4	TYR 48, TRP 20, TRP 219, CYS 298, LEU 301	Hydrogen bond, Pi-Hydrogen bond donor Pi-Sigma, Pi-Sulfur, Pi-Pi stacked, Pi-Alkyl	2.87, 2.00, 3.85, 5.72, 4.47, 5.55, 3.01
Orientin	-9.0	LEU 301, ALA 299, LEU 300, CYS 298, PHE 122	Hydrogen bond, Pi-Sulfur, Pi-Pi stacked	2.00, 2.25, 2.05, 5.16, 3.58, 5.20, 3.80
P-coumaric acid	-6.2	HIS 110, LEU 300, TRP 111, CYS 298	Hydrogen bond, Pi-Sulfur, Pi-Pi T-shaped	2.97, 2.22, 5.04, 4.79
Palbinone	-9.0	TYR 48, CYS 298, TRP 20	Hydrogen bond, Pi-Hydrogen bond donor,	3.04, 3.60, 2.86
Palmatine	-8.3	SER 302, TRP 20, PHE 122, VAL 47, LEU 124, CYS 298, NAP 404	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi stacked, Pi-Alkyl, Alkyl	2.75, 2.70, 5.09, 4.59, 4.62, 3.80, 5.38, 5.11, 3.55
Pistafolin B	-8.7	TYR 48, LYS 21, SER 22, TRP 20, TRP 111, LEU 301, ALA 299, LEU 300, VAL 47	Hydrogen bond, Pi-Alkyl	2.55, 2.28, 2.99, 2.44, 2.58, 2.17, 2.31, 4.88, 5.12
Protocatechualdehyde	-5.3	HIS 110, TYR 48, TRP 111, CYS 298	Hydrogen bond, Pi-Pi T-shaped, Pi-Sulfur	2.21, 2.30, 6.85, 4.96
Protopine	-9.0	LEU 301, CYS 298, LEU 300	Hydrogen bond, Pi-Pi-Sigma, Pi-Sulfur, Pi-Alkyl, Alkyl	1.67, 3.71, 4.73, 3.67, 5.69, 5.17
Puerariafuran	-6.9	TYR 48, TRP 20, NAP 404, CYS 298, PRO 218, VAL 47	Hydrogen bond, Pi-Alkyl, Alkyl	2.13, 2.79, 2.32, 5.36, 5.14, 5.47, 4.54
Quercetin	-8.0	HIS 110, SER 302, LEU 301, NAP 404, TRP 20, VAL 47	Hydroge nbond, Pi-Pi Stacked, Pi-Alkyl	2.13, 2.02, 2.54, 2.69, 2.33, 5.78, 5.69, 5.27
Quercitrin	-9.0	CYS 298, LEU 300, ALA 299, VAL 297, TRP 219, LEU 301	Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl	3.09, 2.32, 2.71, 2.30, 4.55, 5.94, 4.72
Rhetsinine	-9.3	LEU 300, LEU 301, TRP 219, TRP 20, CYS 298, NAP 404	Hydrogen bond, Pi-Cation, Pi-Pi Stacked, Pi-Alkyl	2.95, 1.83, 3.77, 5.89, 6.42, 5.31, 5.16, 5.34
Rosmarinic acid	-8.7	HIS 110, TYR 48, CYS 298, VAL 47, LEU 301, SER 302, PHE 122	Hydrogen bond, Pi-Pi-Sigma, Pi-Pi Stacked	2.24, 2.35, 3.45, 2.24, 3.74, 2.99, 2.63, 4.11
Rutin	-8.4	HIS 110, VAL 47, TRP 20, PHE 121,	Hydrogen bond, Pi-Pi-Sigma, Pi-Pi T-	1.99, 3.05, 3.92, 5.14, 5.53, 7.22, 5.20, 3.80, 4.85, 4.16, 4.32

		TRP 219, LEU 301, ALA 299	shaped, Pi-Pi Stacked, Pi-Alkyl, Alkyl	
Resveratrol	-7.4	HIS 110, TRP 111, CYS 298	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi T-shaped, Pi-Sulfur	2.19, 3.11, 5.03
Scopolin	-7.4	HIS 110, TYR 48, TRP 111, LEU 301, LEU 300, SER 302, VAL 297, VAL 47, PHE 122	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl,	2.14, 2.62, 2.73, 2.70, 2.91, 2.55, 3.71, 5.30, 5.04
Scopoletin	-5.9	HIS 110, TYR 48, TRP 20, CYS 298, PHE 122	Hydrogen bond, Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl	2.16, 2.15, 5.01, 5.57, 5.17, 4.12
Semilicoisoflavone B	-9.0	TRP 111, CYS 298, LEU 300, ALA 299, LEU 301, TRP 219	Hydrogen bond, Pi-Alkyl, Pi-Pi T-shaped,	2.33, 5.42, 2.45, 3.07, 2.83, 5.63, 4.46, 6.74
Syringic acid	-5.9	HIS 110, TYR 48, NAP 404, TRP 20, LEU 300, TRP 219, TRP 111, CYS 298, VAL 47	Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.43, 2.14, 2.42, 5.11, 2.62, 5.23, 5.04, 5.44, 4.99, 3.87, 5.49, 4.39
Trans-anethole	-5.9	LEU 301, HIS 110, TYR 48, NAP 404, PHE 122, LEU 300, CYS 298, TRP 111, TRP 20	Hydrogen bond, Pi-Pi-Sulfur, Pi-Pi Stacked, Pi-Sigma, Pi-Alkyl, Alkyl	3.06, 5.25, 4.99, 4.03, 4.65, 5.20, 5.09, 5.61, 4.10
Tectorigenin	-8.0	HIS 110, TRP 111, CYS 298, LEU 300, ALA 299, TRP 219, LEU 301	Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl, Pi-Pi T-shaped	2.45, 5.41, 4.96, 5.11, 2.24, 2.75, 4.27, 4.23, 5.41
Tiliroside	-9.8	VAL 297, ALA 299, LEU 300, TRP 111, LEU 301, TRP 219	Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl,	1.80, 1.80, 2.46, 2.13, 2.54, 4.63, 4.58, 6.04
Tingenin B	-9.5	HIS 110, TYR 48, NAP 404, TRP 20	Hydrogen bond, Pi-Pi Stacked	2.25, 2.35, 2.67, 5.18
Verbascoside	-8.5	HIS 110, TYR 48, ARG 296, VAL 297, TRP 20, TRP 219, VAL 47, ALA 299, LEU 301	Hydrogen bond, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Sigma, Pi-Alkyl	2.57, 2.64, 2.32, 2.74, 4.89, 4.16, 4.62, 5.38, 3.54
7-O-galloyl-D-sedoheptulose	-6.4	HIS 110, TYR 48, VAL 47, TRP 111,	Hydrogen bond, Pi-Alkyl	3.05, 2.54, 2.11, 4.72, 2.24, 2.30
- (-) epicatechin	-7.5	TRP 111, SER 302, TRP 20, VAL 47	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.07, 1.83, 5.34, 5.11
(+)-trans-decursinol	-7.5	HIS 110, TRP 111, TRP 79, VAL 47	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.46, 2.18, 5.12, 5.66, 4.93, 4.46
2,6-bis (3,4-dihydroxy benzylidene) cyclohexanone	-8.7	HIS 110, LEU 300, ALA 299, TRP 20, TRP 111, LEU 301, CYS 298, TRP 219,	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.95, 2.23, 2.42, 3.29, 5.18, 4.55, 4.45
2,5-bis (3,4-dihydroxy benzylidene) cyclopentanone	-8.3	LEU 300, ALA 299, SER 302, LEU 301, TRP 219, PHE 122	Hydrogen bond, Pi-Pi Stacked, Pi-Sigma, Pi-Alkyl	2.09, 2.75, 2.36, 3.81, 4.52, 3.81
2-(4-hydroxy-3-methoxy phenyl) ethanoic acid	-5.3	HIS 110, LEU 300, TRP 111, CYS 298, TRP 20, PHE 122	Hydrogen bond, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Sulfur, Pi-Alkyl	2.62, 2.49, 2.09, 5.67, 4.89, 5.89, 4.21

Table S2: Interaction of secondary metabolites with 3O3R

Metabolites	Binding Affinity (kcal/mol) 3o3R	Amino acid Residues	Interaction Type	Interaction Distance Å
Apigenin	-10.3	TYR 49, LYS 78, GLN 184, TYR 210, CYS 299, LYS 263, SER 215	Hydrogen bond, Carbon-Hydrogen bond Pi- Donor Hydrogen bond, Pi-Pi stacked, Pi-Alkyl	2.89, 2.30, 6.33, 2.73, 4.03, 4.07, 5.40, 4.51, 2.82
Afzelin	-8.8	HIS 111, TYR 210, GLY 300, TRP 21	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi T-shaped, Pi-Pi stacked, Pi-Alkyl	2.20, 2.93, 2.22, 2.60, 5.48, 5.89, 2.66
Aurantio-obtusin	-7.9	HIS 111, TRP 80, VAL 48, TRP 21	Hydrogen bond, Pi-Pi T-shaped, Pi-Sigma, Pi-Alkyl	2.58, 4.78, 4.94, 4.60, 4.70, 3.71
Allocryptopine	-10.0	HIS 111, GLN 184, TYR 210, ASN 161, ASP 44, ILE 261	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi stacked, Pi-Alkyl, Alkyl	2.13, 3.07, 3.27, 4.15, 4.73, 3.37, 3.30, 3.50, 5.10
Astragallin	-7.9	HIS 111, TYR 49, TRP 21, CYS 299	Hydrogen bond, Pi-Pi stacked, Pi-Sulfur	3.02, 2.24, 2.04, 4.81, 5.91, 5.20
Beta-glucogallin	-8.2	HIS 111, TYR 49, LYS 78, GLN 184, THR 20, ASP 44, SER 211, GLY 300, GLY 19, TYR 210,	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi stacked, Pi-Pi T-shaped	2.26, 2.86, 5.77, 2.70, 2.35, 2.52, 1.92, 1.79, 2.62, 2.17, 3.33, 4.88
Brazilin	-7.3	HIS 111, GLY 300, TRP 80, LEU 301	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.76, 2.13, 4.93, 4.79
Butein	-9.8	HIS 111, SER 211, SER 215, LYS 263, TYR 210, TRP 21, CYS 299	Hydrogen bond, Pi-Donor Hydrogen bond, Pi- Sigma, Pi-Pi stacked, Pi-Pi T-shaped, Pi-Alkyl	1.88, 2.57, 3.01, 1.68, 2.29, 5.40, 3.93, 5.72, 6.78, 4.88
Capillarisin	-9.3	TYR 49, LYS 78, GLN 184, TYR 210, TRP 21, LEU 301, CYS 299, ILE 261, ASP 44, HISS 111	Hydrogen bond, Carbon-Hydrogen bond, Pi-Cation, Pi-Pi stacked, Pi-Pi T-shaped, Pi-Alkyl	2.75, 3.73, 2.64, 2.38, 3.94, 3.82, 5.83, 5.29, 3.58, 4.86
Cinnamaldehyde	-6.9	HIS 111, GLN 184, LYS 78, TRP 21, LYS 263	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.37, 2.15, 2.83, 5.36, 5.34
Cistanoside F	-8.9	HIS 111, ILE 261, SER 215. SER 211, ASN 161, ALA 298, TYR 210	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi stacked	1.97, 2.31, 1.84, 2.32, 3.17, 2.95, 2.26, 4.93
Cuminaldehyde	-7.6	HIS 111, GLN 184, LYS 78, TYR 210	Hydrogen bond, Pi-Pi stacked	2.44, 2.80, 2.18, 4.25
Curcumin	-10.0	HIS 111, SER 215, TYR 210, TRP 21, CYS 299, LYS 263, TYR 220, GLY 300, SER 211, ASP 217	Hydrogen bond, Carbon-Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi stacked, Pi-Alkyl, Alkyl	2.64, 2.13, 1.91, 3.87, 4.50, 4.56, 4.29, 4.91, 3.73, 3.08, 3,59
Caffeic acid	-7.7	TYR 49, LYS 78, LYS 263,	Hydrogen bond, Pi-Pi Stacked	2.43, 2.77, 6.03, 2.19, 1.93, 3.98

		SER 215, TYR 210		
Daidzein	-9.6	HIS 111, SER 211, SER 215, CYS 299, LYS 263	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sulfur, Pi-Alkyl	2.33, 2.17, 3.00, 5.39, 5.63, 4.77
Decursidin	-9.9	HIS 111, TYR 210, GLY 300, VAL 48, TRP 21, CYS 299, ARG 218,	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Alkyl, Alkyl	2.89, 2.37, 3.54, 4.52, 2.81, 4.29, 4.76, 4.76, 4.83, 4.17
Desmanthin -I	-9.9	HIS 111, TYR 49, ALA 298, LYS 78, ASP 44, TYR 210, TRP 21	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi stacked, Pi-Pi T-shaped	2.77, 2.59, 2.27, 2.29, 5.88, 2.47, 4.24, 2.97, 2.59,5.87
Davidigenin	-8.9	HIS 111, LYS 263, ILE 261, TYR 210, TRP 21, CYS 299, SER 211	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Sulfur	2.14, 2.41, 2.52, 2.62, 3.83, 5.10, 5.63, 2.94
Davallialactone	-10.0	HIS 111, ASN 161, TRP 112, SER 215, TRP 21, LYS 263, LEU 301, TRP 80, CYS 299	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.04, 3.08, 3.56, 2.84, 4.65, 4.62, 3.57, 4.38, 4.58
Dehydroglyasperin D	-9.7	HIS 111, ASP 44, GLN 184, TRP 210, TRP 21, TRP 80, LEU 301, TYR 220, LEU 123	Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.27, 2.53, 2.60, 3.89,4.73, 4.60, 4.96, 4.59,3.80
Desmethylanhydroicaritin	-11.2	TYR 49, GLN 184, LYS 78, TYR 210, CYS 299, TRP 21, LYS 263, SER 215	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.87, 2.61, 6.24, 2.38, 4.04, 3.84, 5.48, 3.86, 5.04, 4.50, 4.32, 2.89
Emodin	-7.9	HIS 111, TYR 49, TRP 21, TYR 210, CYS 299	Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl	2.28, 1.85, 2.05, 5.73,4.98, 4.78, 4.72, 4.23, 4.97,
Ellagic acid	-8.9	HIS 111, GLN 184, ASP 44, SER 211, SER 215, TYR 210, CYS 299	Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl	1.88, 5.42, 2.95, 2.35, 2.82, 3.79, 4.48, 4.89, 3.61, 4.00, 5.34
Epiberberin	-8.8	HIS 111, TYR 210, TRP 21, PRO 219, LEU 123	Hydrogen bond, Pi-Pi stacked, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.08, 4.37, 4.93, 5.39, 4.29, 5.45
Ergosterol Peroxide	-8.9	HIS 111, TYR 49, SER 211, SER 215, TYR 210, TRP 21	Hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-shaped	2.54, 3.48, 2.22, 5.78, 3.53, 2.18, 3.74, 5.82,
Eriodictyol	-9.1	HIS 111, ALA 298, TYR 210, TRP 21, CYS 299	Hydrogen bond, Pi-Pi Stacked, Pi-Sulfur	2.66, 2.49, 2.64, 3.75, 5.32, 5.29
Flaviolin	-8.6	TYR 49, LYS 78, GLN 184, TYR 210, CYS 299	Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl	2.75, 5.97, 2.69, 2.37, 2.31, 3.69, 4.36, 4.88
Galloyl Paeoniflorin	-10.5	HIS 111, GLY 300, ALA 298, TYR 220, PRO 219	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl	2.24, 2.84, 2.39, 1.79, 2.92, 5.44, 5.19

Groenlandicine	-10.8	HIS 111, ILE 261, SER 215, TYR 210, LYS 263, CYS 299, ASP 217, TYR 49, SER 211, PRO 212	Hydrogen bond, Carbon-Hydrogen bond Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.19, 5.06, 1.99, 2.04, 3.99, 5.46, 4.10, 4.56, 3.40, 2.57, 2.71, 3.66
Ganoderic acid DF	-10.1	HIS 111, TRP 21, GLN 184, GLN 50, TRP 80, VAL 48	Hydrogen bond, Carbon-Hydrogen bond, Pi-Sigma	2.32, 2.32, 3.53, 2.61, 2.60, 3.60, 3.65
Genistein	-9.9	TYR 49, ILE 261, SER 215, SER 211, HIS 111, CYS 299, TRP 21	Hydrogen bond, Pi-Cation, Pi-Donor Hydrogen bond Pi-Pi T-shaped, Pi-Alkyl	2.39, 2.46, 2.71, 3.20, 2.10, 4.99, 4.93, 4.95, 4.91
Ganomycin B	-9.3	HIS 111, ALA 298, CYS 299, TRP 21, LYS 263, TYR 210, PRO 219	Hydrogen bond Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.60, 2.06, 2.41, 5.40, 4.54, 3.82, 4.11, 4.98, 4.51, 5.33
Gallic acid	-6.6	TYR 49, LYS 78, ASN 161, TYR 210	Hydrogen bond, Pi-Pi Stacked	2.75, 2.76, 2.69, 2.94, 3.76
Gossypol	-9.4	PHE 302, VAL 303, GLY 300, TYR 220	Hydrogen bond, Pi-Pi T-shaped	2.18, 4.95, 2.21, 2.77, 4.81, 5.13,
Hypholomine B	-8.9	HIS 111, ARG 218, ARG 297, TRP 21, TYR 220, ALA 298	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi Stacked, Pi-Pi T-shaped, Pi-Alkyl,	2.79, 4.66, 3.50, 2.91, 5.77, 5.03, 4.68
Isoangustone A	-9.0	HIS 111, TYR 49, GLN 300, TYR 210, PHE 302, TRP 21, TYR 220, VAL 303, CYS 299	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.76, 2.56, 2.25, 5.11, 3.92, 5.47, 5.27, 4.98, 5.37, 4.59, 5.10, 5.27, 5.47, 4.67, 5.05
Isocampneoside II	-10.2	HIS 111, ASP 44, GLY 300, ALA 298, TYR 40, TYR 210, PHE 122, CYS 299, ARG 218, TRP 21, GLY 19	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi Stacked, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.29, 2.58, 2.74, 2.08, 3.55, 2.70, 5.88, 4.56, 4.90, 3.49, 4.35, 4.64, 3.49
Isoquercitrin	-8.7	HIS 111, ASN 161, ALA 298, TRP 21	Hydrogen bond, Pi-Pi T-shaped	2.29, 2.57, 2.31, 2.03, 4.94
Isovitexin	-8.1	HIS 111, TYR 49, ASN 161, TRP 80, LEU 123, LEU 301	Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl,	1.94, 2.94, 2.57, 1.77, 2.29, 5.46, 5.12, 4.37, 3.93
Isoliquiritigenin	-9.5	HIS 111, GLY 300, ASN 161, LYS 263, TYR 210, TRP 21, CYS 299, SER 211	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl	1.18, 2.99, 2.16, 2.98, 2.49, 3.88, 6.70, 4.83, 3.05
Irigenin	-9.0	HIS 111, TYR 49, LYS 78, GLY 300, TRP 21, TYR 210, ASP 44, LEU 301, TRP 80, CYS 299, LYS 263	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.17, 2.86, 6.14, 2.13, 5.67, 4.14, 3.52, 4.66, 4.59, 4.50, 3.98, 4.25

Jateorrhizine	-9.7	HIS 111, SER 215, TYR 210, LYS 263, CYS 299, LEU 301, TRP 80, VAL 48, TYR 49, SER 211, PRO 212, ASP 217, GLY 300	Hydrogen bond, Pi-Sigma, Carbon-Hydrogen bond, Pi-Donor Hydrogen bond Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.44, 4.10, 2.03, 3.96, 4.15, 4.49, 4.76, 5.43, 5.07, 2.48, 2.76, 3.70, 3.54, 3.33
Kakkalide	-10.1	HIS 111, ASP 217, SER 211, GLY 300, TYR 49, TYR 220, CYS 299, VAL 48, TRP 80	Hydrogen bond, Carbon-Hydrogen bond, Pi-Donor Hydrogen bond Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.86, 2.78, 2.80, 4.08, 2.45, 2.37, 2.84, 3.02, 2.76, 5.22, 3.84, 4.77, 4.93, 5.00
Kurarinol	-8.8	HIS 111, CYS 299, TRP 21, VAL 48, TYR 210, TYR 220, PRO 219, ARG 218	Hydrogen bond, Pi-Sigma, Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.03, 2.93, 5.19, 2.48, 3.90, 5.22, 4.32, 2.52, 4.13, 4.28, 4.68, 4.14, 3.85
Kurarinone	-8.9	HIS 111, TRP 21, VAL 48, CYS 299, ARG 218, TYR 220, PRO 219, TYR 210	Hydrogen bond, Pi-Sigma, Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.03, 2.66, 3.89, 5.27, 4.35, 2.33, 4.23, 5.29, 3.86, 4.81, 4.35, 4.26
Kushenol E	-8.4	HIS 111, GLY 300, TYR 210, TRP 80, TRP 21, TYR 220, LEU 301, VAL 48	Hydrogen bond, Pi-Sigma, Carbon-Hydrogen bond, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.84, 4.51, 3.61, 3.84, 3.65, 3.92, 6.19, 5.50, 5.47, 3.96
Licochalcone A	-7.5	TYR 49, TRP 21, TYR 220, HIS 111, TYR 210	Hydrogen bond, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Alkyl	2.59, 4.33, 5.07, 5.30, 4.23
Loganin	-8.8	HIS 111, SER 215, SER 211, GLY 300	Hydrogen bond,	2.44, 2.44, 2.06, 2.42, 2.05
Lucidin	-10.3	HIS 111, TYR 49, LYS 78, GLN 184, THR 20, TYR 21, TYR 210, CYS 299	Hydrogen bond Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Alkyl	2.67, 2.64, 2.84, 2.71, 2.60, 2.19, 5.37, 4.31, 3.77, 4.71, 5.17, 5.04
Luteolin	-10.0	HIS 111, LYS 78, GLN 184, ASP 44, GLY 300, CYS 299, TYR 210, TRP 21	Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Pi Stacked	2.64, 2.31, 5.46, 2.32, 1.95, 2.08, 3.86, 4.33, 4.01, 4.78
Lucidumol A	-9.8	HIS 111, TYR 49, ASN 161, TYR 210	Hydrogen bond, Pi-Sigma	2.03, 2.08, 2.50, 3.59
Maesanin	-7.9	TYR 49, SER 211, SER 215, HIS 111, TRP 80, TRP 21, VAL 48, TRP 112, TYR 210, LEU 301, GLY 19	Hydrogen bond, Carbon-Hydrogen bond, Pi-Alkyl, Alkyl	2.07, 2.41, 2.12, 1.72, 2.70, 5.12, 5.02, 4.77, 4.88, 4.85, 5.46, 5.05, 4.06, 5.37, 3.08
Methyl lucidenate F	-9.4	HIS 111, TRP 21, LEU 123, PHE 122	Hydrogen bond, Pi-Sigma	2.07, 3.85, 2.79, 1.85, 2.09
Myrciaphenone B	-9.5	HIS 111, ASN 161, SER 211,	Hydrogen bond, Carbon-Hydrogen	2.77, 2.63, 2.34, 2.17, 2.86, 5.05, 4.69

		LYS 78, TYR 210, TRP 21, CYS 299	bond, Pi-Pi T-shaped, Pi-Pi Stacked	
Naringenin	-10.0	HIS 111, TYR 49, LYS 78, GLN 184, ASP 44, TYR 210, CYS 299	Hydrogen bond, Pi-Sigma, Pi-Pi Stacked	2.68, 2.75, 2.43, 5.42, 2.23, 4.35, 3.91
Nodakenin	-10.2	TYR 49, LYS 78, GLN 184, TYR 210, CYS 299, LYS 263, SER 215	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl	2.84, 6.31, 2.74, 5.39, 4.02, 5.40, 4.55, 2.77
Orientin	-9.0	TYR 49, TRP 21, CYS 299, ARG 218	Hydrogen bond, Pi-Sulfur, Pi-Pi Stacked, Pi-Alkyl	2.77, 5.30, 4.47, 5.67, 4.88, 5.32
P-coumarinic acid	-7.6	ILE 261, THR 20, TRP 21, TYR 210, HIS 111	Hydrogen bond, Pi-Cation, Pi-Pi Stacked	2.13, 2.76, 1.97, 3.73, 4.36
Palbinone	-10.0	HIS 111, ASN 161, TRP 21	Hydrogen bond, Pi-Sigma	1.89, 3.83, 2.99, 2.72, 3.55
Palmatine	-7.0	HIS 111, TRP 21, TRP 112, TRP 80, TYR 49, VAL 48	Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl	2.69, 2.33, 4.23, 3.97, 5.10, 5.12, 5.12, 5.46, 5.07
Pistafolin B	-9.9	TYR 49, THR 20, TRP 21, LYS 78, GLY 300, ASP 217, TYR 210, LYS 263, SER 215, HIS 111	Hydrogen bond, Pi-Donor Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Alkyl	2.85, 2.88, 2,24, 2.96, 5.94, 2.93, 2.23, 1.96, 2.38, 3.90, 3.77, 3.36, 2.66
Protocatechualdehyde	-9.0	TYR 49, LYS 78, ASP 44, THR 20, SER 211, SER 215	Hydrogen bond,	2.61, 2.82, 1.75, 1.95, 2.15, 1.82
Protopine	-8.3	HIS 111, TRP 21, VAL 48, ASN 161	Hydrogen bond, Carbon-Hydrogen bond, Pi-Alkyl	2.84, 2.53, 5.01, 3.16
Puerariafuran	-7.3	HIS 111, TYR 49, GLY 300, TRP 44, CYS 299	Hydrogen bond, Carbon-Hydrogen bond, Pi-Sulfur, Pi-Pi Stacked	2.28, 2.50, 2.21, 5.18, 5.03, 5.65
Quercetin	-10.6	TYR 49, LYS 78, GLN 184, ASP 217, SER 215, TYR 210, TRP 21, LYS 263, CYS 299	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Alkyl	2.86, 6.31, 2.35, 2.74, 2.07, 2.83, 5.38, 4.09, 3.87, 4.31, 5.43
Quercitrin	-10.6	VAL 48, TRP 21, GLY 300, PRO 219	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Alkyl	2.50, 3.02, 3.76, 2.68, 1.96, 5.45
Rhetsinine	-10.6	HIS 111, TRP 80, TYR 210, TRP 21, VAL 48, LEU 123	Hydrogen bond, Pi-Cation, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Alkyl	2.15, 5.58, 3.01, 6.33, 4.34, 3.83, 4.57, 5.03, 4.98, 5.46
Rosmarinic acid	-9.8	HIS 111, LYS 78, SER 211, SER 215, ILE 261, TYR 210, TRP 21	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi Stacked	1.96, 2.23, 2.51, 2.92, 1.69, 2.43, 3.76, 4.61
Rutin	-8.5	HIS 111, ASN 161, TYR 210, VAL 303, TRP 21, LEU 123	Hydrogen bond, Pi-Sigma, Pi-Alkyl	2.34, 2.61,2.71, 2.03, 2.37, 5.40, 2.11, 3.75

Resveratrol	-9.2	TYR 49, LYS 78, TYR 210, LYS 263	Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl	2.90, 6.14, 4.10, 2.85
Scopolin	-8.3	HIS 111, TRP 21, SER 215, TYR 210, CYS 299	Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl	2.18, 2.72, 1.80, 3.96, 3.85, 5.24, 1.77
Scopoletin	-8.8	TYR 49, LYS 78, GLN 184, ILE 261, SER 215, TYR 210, LYS 263, ASP 217, SER 211	Hydrogen bond, Pi-Sigma, Pi-Donor Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl, Carbon-Hydrogen bond, Alkyl	2.58, 5.87, 2.48, 2.14, 1.97, 3.96, 4.18, 5.43,4.12, 3.30, 2.69
Semilicoisoflavone B	-8.7	HIS 111, TRP 21, LYS 22, TRP 80, LEU 301, VAL 48	Hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl, Alkyl	2.86, 2.47, 5.13, 2.13, 5.18, 2.82, 4.93, 5.16, 5.00, 4.89, 4.82
Syringic acid	-5.8	HIS 111, LYS 78, SER 215, SER 211, SER 160, TRP 21, TYR 210, CYS 299	Hydrogen bond, Carbon-Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl	2.11, 2.48, 4.30, 2.76, 2.54, 2.06, 3.47, 3.87, 4.12, 4.14, 5.08,
Trans-anethole	-6.9	HIS 111, TYR 210, ASN 161, LYS 263	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl, Alkyl	2.24, 4.64, 3.58, 3.76, 3.44, 4.62
Tectorigenin	-8.9	HIS 111, TYR 210, TRP 21, CYS 299, GLY 19	Hydrogen bond, Carbon-Hydrogen bond, Pi-Sulfur, Pi-Pi Stacked	2.48, 2.51, 4.50, 5.37, 5.01, 4.87, 3.55
Tiliroside	-9.1kcal/mol	HIS 111, GLY 300, ALA 298, LEU 301, TRP 80, LEU 123, SER 211,	Hydrogen bond, Carbon-Hydrogen bond, Pi-Donor Hydrogen bond, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl,	2.00, 2.75, 3.20, 2.81, 2.60, 3.55, 4.67, 4.84, 5.44, 4.33, 3.25
Tingenin B	-10.1	HIS 111, GLN 50, TRP 21	Hydrogen bond, Pi-Sigma,	2.30, 2.76, 3.79
Verbascoside	-9.8	HIS 111, TRP 21, TYR 220, TYR 210, TYR 49, ARG 218	Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-shaped, Pi-Alkyl	2.15, 3.65, 5.12, 5.88, 4.54, 5.43
7-O-galloyl-D-sedoheptulose	-8.3	HIS 111, TYR 49, TRP 21, ASP 217, LYS 78, ASN 161, GLY 19, TYR 210, LYS 263	Hydrogen bond, Carbon-Hydrogen bond, Pi-Sigma, Pi-Alkyl	1.85, 2.55, 2.65, 2.27, 1.79, 2.22, 3.57, 3.74, 3.94
- (-) epicatechin	-9.1	HIS 111, THR 20, ILE 261, GLY 19, TYR 210, TYR 49, TRP 21	Hydrogen bond, Carbon-Hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-shaped	2.87, 3.37, 2.35, 2.27, 3.24, 3.52, 5,78, 5.78
(+)-trans-decursinol	-8.6	HIS 111, TYR 210, LEU 301, VAL 48	Hydrogen bond, Pi-Alkyl	2.22, 2.39, 3.01, 4.72
2,6-bis (3,4-dihydroxy benzylidene) cyclohexanone	-11.0	TYR 49, LYS 78, LYS 263, SER 211, TYR 210, PRO 212, PRO 216, LEU 213, TRP 21	Hydrogen bond, Carbon-Hydrogen bond, Pi-Pi Stacked, Pi-Alkyl. Alkyl	2.74, 6.14, 4.07, 4.43, 5.23, 2.25, 3.04, 4.17, 3.25, 4.20, 5.27, 5.24
2,5-bis (3,4-dihydroxy benzylidene) cyclopentanone	-10.0	HIS 111, GLY 300, SER 211, LYS 263, SER	Hydrogen bond, Pi-donor Hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl.	1.91, 1,95, 2.28, 2.26, 1.79, 3.62, 5.30

		215, TYR 210, LEU 301		
2-(4-hydroxy-3-methoxy phenyl) ethanoic acid	-7.1	TYR 49, LYS 78, SER 215, SER 211, ASP 217, TYR 210, TRP 21	Hydrogen bond, Pi-Pi T-shaped, Pi-Pi Stacked, Pi-Alkyl.	2.85, 5.93, 6.21, 1.90, 3.45, 2.80, 4.36, 5.30, 4.61

Table S3: ADMET analysis of secondary metabolites

Secondary metabolites	Absorption				Distribution			Metabolism					Excretion				Toxicity
	Water solubility (Log mol/L)	$CaCO_2$ Permeability (Log Papp 10^{-6} cm/s)	Intestinal absorption (% absorbed)	Skin permeability (log Kp)	VDss(Human, log L/kg)	BBB permeability (log BB)	CNS permeability (log PS)	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Total clearance	Renal OCT2 substrate clearance	Ames Toxicity	Hepato Toxicity	Rat Oral Toxicity (LD_{50})
Epalrestat	-3.144	1.31	89.553	-2.735	-0.667	0.108	-2.323	No	No	No	No	No	0.11	No	No	No	3.006
Apigenin	-3.329	1.007	93.25	-2.735	0.822	-0.734	-2.061	Yes	Yes	No	No	No	0.566	No	No	No	2.45
Afzelin	-2.969	0.123	60.006	-2.735	1.15	-1.265	-3.994	No	No	No	No	No	0.431	No	No	No	2.61
Aurantio-obtusin	-3.287	0.158	83.987	-2.738	0.329	-1.076	-3.23	No	No	No	No	No	0.29	No	No	No	1.643
Allocryptopine	-4.06	1.06	97.744	-3.014	0.669	-0.536	-2.091	Yes	No	No	No	No	0.904	Yes	No	No	2.977
Astragallin	-2.863	0.306	48.052	-2.735	1.444	-1.514	-3.908	No	No	No	No	No	0.462	No	No	No	2.546
Beta-glucogallin	-1.89	-0.795	37.36	-2.735	0.517	-1.616	-4.465	No	No	No	No	No	0.512	No	No	No	2.414
Brazillin	-3.339	0.259	94.651	-2.735	0.686	-0.62	-2.497	Yes	Yes	No	No	No	0.083	No	No	No	2.401
Butein	-3.177	-0.021	72.567	-2.736	0.741	-0.895	-2.395	Yes	No	No	No	No	0.015	No	No	No	2.456

Capillarisin	-3.383	-0.181	93.142	-2.736	0.274	-1.329	-3.286	Yes	No	Yes	No	No	0.466	No	No	No	2.281
Cinnamaldehyde	-2.175	1.634	95.015	-2.355	0.266	0.436	-1.582	Yes	No	No	No	No	0.203	No	No	No	1.88
Cistanoside F	-2.654	0.063	48.492	-2.735	0.784	-1.742	-4.743	No	No	No	No	No	1.027	No	No	No	2.6
Curcumin	-4.01	-0.093	82.19	-2.764	-0.215	-0.562	-2.99	Yes	Yes	Yes	No	Yes	-0.002	No	No	No	1.833
Cuminaldehyde	-2.966	1.609	95.844	-1.196	0.324	0.438	-1.485	Yes	No	No	No	No	0.227	No	No	No	1.7
Caffeic acid	-2.33	0.634	69.407	-2.722	-1.098	-0.647	-2.608	No	No	No	No	No	0.508	No	No	No	2.383
Daidzein	-3.793	0.903	94.839	-2.748	-0.172	-0.064	-1.992	Yes	Yes	Yes	No	No	0.164	No	No	No	2.164
Decursidin	-5.236	0.946	100	-2.893	-0.29	-0.866	-2.894	No	Yes	No	No	Yes	0.87	No	No	Yes	3.127
Desmanthin-1	-2.892	-1.36	25.792	-2.735	0.508	-2.745	-4.806	No	No	No	No	No	0.217	No	No	No	2.484
Davidigenin	-3.055	0.95	91.284	-2.751	0.534	-0.736	-2.321	Yes	Yes	No	No	No	0.187	No	No	No	2.424
Davallialactone	-3.148	0.019	68.809	-2.735	0.71	-1.702	-3.449	No	No	No	No	No	-0.003	No	No	No	2.375
Dehydroglyasperin D	-4.233	0.733	92.326	-2.781	0.298	-0.261	-2.061	No	Yes	Yes	No	Yes	0.441	No	No	No	2.323
Desmethylanhydroic aritin	-3.347	0.078	82.007	-2.735	0.182	-1.266	-2.337	Yes	Yes	Yes	No	Yes	0.258	No	No	No	2.42
Emodin	-3.192	0.055	74.485	-2.737	0.456	-0.727	-2.336	Yes	No	No	No	No	0.344	No	No	No	2.116
Ellagic acid	-3.181	0.335	86.684	-2.735	0.375	-1.272	-3.533	Yes	No	No	No	No	0.537	No	No	No	2.399
Engeletin	-3.188	0.408	58.658	-2.735	1.122	-0.991	-4.014	No	No	No	No	No	0.046	No	No	No	2.531

Epiberberine	-3.615	1.87	97.961	-2.553	0.887	0.341	-1.557	Yes	No	No	Yes	No	1.278	Yes	No	Yes	2.652
Ergosterol peroxide	-6.096	1.177	94.682	-3.405	0.552	0.489	-2.628	No	No	No	No	No	0.592	No	No	Yes	1.847
Eriodictyol	-3.253	-0.094	74.687	-2.735	0.377	-0.827	-3.142	No	No	No	No	No	-0.013	No	No	No	2.03
Flaviolin	-2.042	0.215	62.173	-2.771	0.313	-0.776	-3.294	No	No	No	No	No	0.425	No	No	No	1.544
Galloyl Paeoniflorin	-2.911	-0.818	54.199	-2.735	1.334	-2.165	-4.848	No	No	No	No	No	-0.125	No	No	No	2.591
Groenlandicine	-3.621	1.275	96.539	-2.783	0.872	0.119	-2.032	Yes	No	No	Yes	No	1.254	No	No	No	2.311
Ganoderic acid DF	-3.946	0.644	66.679	-2.737	-0.619	-0.969	-3.005	No	No	No	No	No	0.259	No	No	No	2.642
Genistein	-3.595	0.9	93.387	-2.735	0.094	-0.71	-2.048	Yes	Yes	No	No	No	0.151	No	No	No	2.268
Ganomycin B	-3.183	0.562	95.475	-2.735	-1.39	-0.934	-2.396	No	No	No	No	No	1.188	No	No	No	2.591
Gallic acid	-2.56	-0.081	43.374	-2.735	-1.855	-1.102	-3.74	No	No	No	No	No	0.518	No	No	No	2.218
Gossypol	-2.93	-0.677	89.39	-2.735	-1.76	-1.459	-2.866	No	No	No	No	No	-0.735	No	Yes	No	2.601
Hypholomine B	-2.958	0.131	86.343	-2.735	0.833	-1.415	-3.591	No	No	No	No	Yes	0.175	No	No	No	2.651
Isoangustone A	-3.576	-0.116	89.78	-2.735	-0.464	-1.025	-1.929	Yes	Yes	Yes	No	No	0.259	No	No	No	2.557
Isocampneoside II	-2.894	-1.602	9.908	-2.735	1.96	-2.181	-4.838	No	No	No	No	No	0.435	No	No	No	2.514
Isoquercitrin	-2.925	0.242	47.999	-2.735	1.846	-1.688	-4.093	No	No	No	No	No	0.394	No	No	No	2.541
Isovitexin	-2.812	-0.618	64.729	-2.735	1.239	-1.375	-3.754	No	No	No	No	No	0.442	No	No	No	2.558
Isoliquiritigenin	-3.06	0.955	91.096	-2.752	0.485	-0.717	-2.205	Yes	Yes	No	No	No	0.087	No	No	No	2.427
Irigenin	-3.385	-0.191	86.383	-2.736	-0.111	-1.338	-3.493	Yes	Yes	Yes	No	Yes	0.518	No	No	No	2.297
Jateorrhizine	-3.871	1.234	94.465	-2.741	0.539	-0.15	-2.142	Yes	No	No	Yes	No	1.222	No	No	Yes	2.445
Kakkalide	-2.85	-1.001	18.162	-2.735	0.626	-1.957	-4.506	No	No	No	No	No	0.118	No	No	No	2.593

Kurarinone	-3.807	0.534	88.068	-2.736	0.361	-1.183	-2.75	No	Yes	Yes	No	Yes	0.48	No	No	No	2.096
Kurarinol	-3.779	0.399	79.348	-2.736	0.589	-1.325	-3.162	No	No	Yes	No	Yes	0.411	No	No	No	2.236
Kushenol E	-3.716	0.264	79.982	-2.735	0.023	-1.096	-2.62	No	Yes	Yes	No	Yes	0.21	No	No	No	2.25
Loganin	-2.614	0.386	39.283	-2.766	0.088	-1.284	-3.745	No	No	No	No	No	1.312	No	No	No	2.214
Lucidin	-2.854	-0.048	87.346	-2.742	0.294	-0.703	-2.528	No	No	No	No	No	0.051	No	No	No	1.909
Luteolin	-3.094	0.096	81.13	-2.735	1.153	-0.907	-2.251	Yes	No	Yes	No	No	0.495	No	No	No	2.455
Lucidumol A	-5.803	0.825	95.381	-3.603	-0.239	-0.001	-1.725	No	No	No	No	No	0.29	No	No	No	3.662
Luteolin-7-rutinoside	-2.904	-1.523	25.033	-2.735	2.023	-1.979	-4.889	No	No	No	No	No	-0.226	No	No	No	2.515
Luteolin-7-O-glucoside	-2.716	0.248	37.556	-2.735	0.884	-1.564	-3.93	No	No	No	No	No	0.478	No	No	No	2.547
Licochalcone A	-4.528	0.699	91.243	-2.837	0.313	-0.183	-2.098	Yes	Yes	Yes	No	Yes	0.449	No	No	No	2.227
Myrciacitrin IV	-2.972	-0.193	60.015	-2.735	1.632	-2.013	-3.982	No	No	No	No	No	-0.227	No	No	No	2.554
Methyl lucidenate F	-4.575	0.904	96.942	-3.329	-0.107	-0.557	-2.775	No	No	No	No	No	0.288	No	No	No	2.169
Myrciaphenone B	-2.912	-1.116	27.617	-2.735	1.582	-1.98	-4.419	No	No	No	No	No	0.536	No	No	No	2.479
Maesanin	-6.256	0.307	90.053	-2.919	-0.015	-0.426	-2.624	No	No	No	No	No	1.768	No	No	No	1.886
Naringenin	-3.224	1.029	91.31	-2.742	-0.015	-0.578	-2.215	Yes	No	No	No	No	0.06	No	No	No	1.791
Nodakenin	-2.882	0.542	45.017	-2.847	-0.393	-1.25	-3.565	No	No	No	No	No	0.447	No	No	Yes	2.622
Orientin	-2.905	-1.25	43.733	-2.735	1.486	-1.639	-4.018	No	No	No	No	No	0.374	No	No	No	2.572
P-coumaric acid	-2.378	1.21	93.494	-2.715	-1.151	-0.225	-2.418	No	No	No	No	No	0.662	No	No	No	2.155

Palbinone	-4.604	0.926	93.095	-4.261	0.147	0.125	-1.808	No	No	No	No	No	0.415	Yes	No	No	2.288
Palmatine	-4.194	0.863	97.084	-2.554	0.641	-0.112	-1.535	Yes	No	No	Yes	No	1.246	No	Yes	Yes	2.551
Pistafolin B	-2.898	-1.359	7.007	-2.735	1.749	-2.265	-4.757	No	No	No	No	No	0.544	No	No	No	2.548
Piperlongumine	-3.228	1.173	94.997	-3.16	-0.08	-0.012	-2.618	No	No	No	No	No	0.215	No	No	Yes	2.449
Protocatechualdehyde	-1.079	1.142	79.385	-3.049	-0.058	-0.389	-2.865	No	No	No	No	No	0.523	No	No	No	1.863
Protopine	-3.825	1.065	97.593	-3.064	0.696	-0.226	-1.977	Yes	Yes	No	No	No	0.936	Yes	Yes	No	2.993
Puerariafuran	-3.744	1.089	93.862	-2.741	-0.15	-0.108	-2.228	Yes	Yes	Yes	No	Yes	0.603	No	No	No	2.349
Quercetin	-2.925	-0.229	77.207	-2.735	1.559	-1.098	-3.065	Yes	No	No	No	No	0.407	No	No	No	2.471
Quercitrin	-2.903	0.048	52.709	-2.735	1.517	-1.495	-4.156	No	No	No	No	No	0.364	No	No	No	2.586
Rhetsinine	-4.195	0.842	92.195	-2.862	0.001	0.349	-1.952	Yes	Yes	Yes	No	No	0.34	No	No	Yes	2.259
Rosmarinic acid	-3.059	-0.937	32.516	-2.735	0.393	-1.378	-3.347	No	No	No	No	No	0.25	No	No	No	2.811
Rutin	-2.892	-0.949	23.446	-2.735	1.663	-1.899	-5.178	No	No	No	No	No	-0.369	No	No	No	2.491
Resveratrol	-3.178	1.17	90.935	-2.737	0.296	-0.048	-2.067	Yes	Yes	No	No	No	0.076	No	Yes	No	2.529
Scopolin	-2.21	0.377	48.119	-2.822	-0.611	-1.286	-3.954	No	No	No	No	No	0.716	No	No	No	2.391
Scopoletin	-2.504	1.184	95.277	-2.944	0.034	-0.299	-2.32	Yes	No	No	No	No	0.73	No	No	No	1.95
Scolymoside	-2.889	-1.188	16.948	-2.735	1.379	-1.96	-4.96	No	No	No	No	No	-0.215	No	No	No	2.501
Semilicoisoflavone B	-3.485	0.403	98.022	-2.735	0.486	-0.937	-1.96	Yes	Yes	Yes	No	No	0.121	No	No	No	2.404

Syringic acid	-2.223	0.495	73.076	-2.735	-1.443	-0.191	-2.701	No	No	No	No	No	0.646	No	No	No	2.157
Trans-anethole	-2.936	1.669	95.592	-1.139	0.343	0.529	-1.659	Yes	No	No	No	No	0.268	No	No	No	1.798
Tectorigenin	-3.435	-0.132	84.511	-2.735	0.166	-1.06	-2.404	Yes	Yes	Yes	No	No	0.132	No	No	No	2.33
Tingenin B	-5.506	0.602	93.537	-3.602	-0.107	0.153	-1.516	No	No	No	No	No	0.113	No	No	Yes	2.322
Tiliroside	-2.918	-0.071	60.065	-2.735	0.655	-1.609	-4.263	No	No	No	No	No	-0.197	No	No	No	2.578
Verbascoside	-2.906	0.096	32.119	-2.735	2.255	-1.86	-4.601	No	No	No	No	No	0.479	No	No	No	2.527
7-O-galloyl-D-sedoheptulose	-1.951	-0.875	11.978	-2.735	0.326	-1.914	-4.617	No	No	No	No	No	0.757	No	No	No	2.347
(-)-Epicatechin	-3.117	-0.283	68.829	-2.735	1.027	-1.054	-3.298	No	No	No	No	No	0.183	No	No	No	2.428
(+)-trans-decursidinol	-2.989	0.504	96.449	-2.855	0.754	0.162	-2.908	No	No	No	No	No	0.595	No	No	No	2.055
2,6-bis (3,4-dihydroxy benzylidene) cyclohexanone	-3.289	0.146	75.738	-2.735	0.693	-0.994	-1.989	Yes	Yes	Yes	No	No	-0.073	No	No	No	2.357
2,5-bis (3,4-dihydroxy benzylidene) cyclopentanone	-3.276	0.08	74.906	-2.735	0.645	-0.97	-2.083	Yes	Yes	Yes	No	No	-0.08	No	No	No	2.34
2-(4-hydroxy-3-methoxy phenyl) ethanoic acid	-2.453	0.265	86.286	-2.722	-1.533	-0.312	-2.723	No	No	No	No	No	0.246	No	No	No	2.252

Table S4: Toxicity profile of Secondary Metabolites

Secondary Metabolites	Plants sources	IC_{50} value	LD_{50}(mg/kg)	Toxicity Class	Active Target	Probability
Apigenin	*Artemisia montana*	0.67	2500	5	Aryl Hydrocarbon Receptor (AhR) Aromatase Estrogen Receptor Alpha(ER) Estrogen Receptor ligand Binding Domain(ER-LBD) Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Suppressor) p53 ATPase family AAA domain-containing protein 5 (ATAD5)	1.0 0.61 1.0 1.0 1.0 1.0 1.0 0.96
Afzelin	*Melastoma sanguineum*	0.81	5000	5	Carcinogenicity Immunotoxicity Aryl hydrocarbon receptor(AhR)	0.50 0.92 0.55
Apiopaeonoside	*Paeonia suffruticosa*	>50	5000	5	Immunotoxicity	0.99
Aurantio-obtusin	*Cassia tora*	15.9	5000	5	Immunotoxicity Mutagenicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha (ER) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Suppressor) p53	0.87 0.61 0.61 0.53 0.85 0.57
Allocryptopine	*Glaucium aleppicum*	27.9	940	4	Carcinogenicity Immunotoxicity Mutagenicity Cytotoxicity	0.60 0.97 0.54 0.52
Astragallin	*Melastoma sanguineum*	5.09	5000	5	Phosphoprotein (Tumor Suppressor) p53	0.50
Beta-glucogallin	*Emblica officinalis*	17	2260	5	-------	------
Brazillin	*Caesalphinia sappan*	100	800	4	------	------
Butein	*Rhus Verniciflua*	0.7	1000	4	Carcinogenicity Immunotoxicity Aryl hydrocarbon Receptor (AhR) Aromatase Estrogen Receptor Alpha (ER)	0.54 0.95 0.72 0.68 0.96 0.91

					Estrogen Receptor Ligand Binding Domain (ER-LBD) Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf/ARE) Heat shock factor response element (HSE) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Supressor) ATPase family AAA domain-containing protein 5 (ATAD5)	0.63 0.63 0.97 0.94 0.66
Capillarisin	*Artemisiae capillari*	0.22 (RLAR)	3800	5	Immunotoxicity Aryl hydrocarbon Receptor (AhR) Mitochondrial Membrane Potential (MMP)	0.81 0.69 0.60
Cinnamaldehyde	*Cinnamomum cassia*	(0.003mg/ml) 0.022	1850	4	Mutagenicity	0.72
Cistanoside F	*Paulownia coreana*	61.52	5000	5	Immunotoxicity	0.94
Curcumin	*Curcuma longa*	6.8	2000	4	Immunotoxicity Estrogen Receptor Alpha (ER) Peroxisome Proliferator Activated Receptor Gamma Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element(nrf/ARE) Heat shock factor response element (HSE) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Supressor) p53	0.92 0.51 1.0 1.0 1.0 1.0 1.0
Cuminaldehyde	*Cuminum cyminum*	(0.00080 mg/ml) 0.0053	1320	4	-----	----
Caffeic acid	*Paulownia coreana*	210.28	2980	5	Carcinogenicity	0.78

					Androgen Receptor(AR)	1.0
D-glaucine	*Corydalis racemose*	16.5% at 50μM	350	4	Immunotoxicity Mutagenicity Cytotoxicity	0.99 0.56 0.52
Daidzein	*Maackia amurensis*	151.9	2430	5	Aryl hydrocarbon Receptor (AhR) Aromatase Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) ATPase family AAA domain-containing protein 5 (ATAD5)	1.0 0.71 1.0 1.0 0.91 1.0
Decursidin	*Angelica decursiva*	6.01±0.23 (HRAR)	832	4	Immunotoxicity	0.91
Desmanthin-1	*Myrcia multiflora*	0.082 (8.2×10^{-8}M)	5000	5	Immunotoxicity	0.99
Davidigenin	*Aremisia dracunculus*	12.70	1190	4	Hepatotoxicity Immunotoxicity Aromatase Estrogen Receptor Alpha(ER) Estrogen Receptor Ligand Binding Domain (ER-LBD)	0.69 0.96 1.0 0.99 1.0
Davallialactone	*Phellinus linteus*	0.33 (RLAR) 0.56 (HRAR)	200	3	Immunotoxicity Aryl hydrocarbon Receptor (AhR)	0.95 0.50
Dehydroglyasperin D	*Glycyrrhiza uralensis*	62.4/176.2	500	4	Immunotoxicity	0.99
Desmethylanhydroicaritin	*Sophora flavescens*	0.95	3919	5	Aryl hydrocarbon Receptor (AhR) Mitochondrial Membrane Potential (MMP)	0.66 0.79
Emodin	*Cassia tora*	15.9	5000	5	Mutagenicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD)	0.93 1.0 1.0 1.0 0.99

					Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Supressor) p53	1.0
Ellagic acid	*Myrciaria dubia*	0.27 (HRAR) 0.047 (RLAR)	2991	4	Carcinogenicity	0.59
Epiberberine	*Coptis chinesis*	100.1 (RLAR)	200	3	Carcinogenicity Immunotoxicity Mutagenicity Cytotoxicity Aryl hydrocarbon Receptor (AhR) Mitochondrial Membrane Potential (MMP)	0.56 0.98 0.62 0.96 0.87 0.87
Ergosterol peroxide	*Ganoderma applanatum*	(15.4 μg/mL) 35.93	2340	5	Immunotoxicity Mutagenicity	0.95 0.50
Eriodictyol	*Chrysanthemum indicum*	7.7	2000	4	Carcinogenicity Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP)	0.57 0.64 0.57 0.73
Flaviolin	*Maesa lanceolata*	10	707	4	Immunotoxicity Mutagenicity Aryl hydrocarbon Receptor (AhR) Mitochondrial Membrane Potential (MMP)	0.57 0.76 0.69 0.66
Galloyl Paeoniflorin	*Paeonia suffruticosa*	44.6	2260	5	Immunotoxicity	0.59
Groenlandicine	*Coptis chinensis*	45.2 (RLAR) 51.2 (HRAR)	200	3	Carcinogenicity Immunotoxicity Mutagenicity Aryl hydrocarbon Receptor (AhR) Mitochondrial Membrane Potential (MMP)	0.54 0.99 0.58 0.73 0.66
Ganoderic acid DF	*Ganoderma lucidum*	22.8	9000	6	Carcinogenicity Immunotoxicity Cytotoxicity Androgen Receptor(AR)	0.55 0.50 0.53 0.62

					Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf/ARE) Heat shock factor response element (HSE)	0.56 0.56
Genistein	*Maackia amurensis*	57.1	2500	5	Aryl hydrocarbon Receptor (AhR) Aromatase Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf/ARE) Heat shock factor response element (HSE) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Supressor) p53 ATPase family AAA domain-containing protein 5 (ATAD5)	1.0 0.82 1.0 1.0 0.69 0.69 0.99 1.0 1.0
Ganomycin B	*Ganoderma lucidum*	25.1	1000	4	Immunotoxicity Mitochondrial Membrane Potential (MMP)	0.64 0.54
Gallic acid	*Eleusine coracana*	(97.3µglml) 571.94	2000	4	Carcinogenicity	0.56
Gossypol	*Gossypium sp.*	0.5	325	4	Immunotoxicity Membrane Potential (MMP) ATPase family AAA domain-containing protein 5 (ATAD5)	0.55 0.99 1.0
Hypholomine B	*Phellinus linteus*	0.82 (RLAR) 1.28 (HRAR)	400	4	Carcinogenicity Immunotoxicity	0.66 0.84
Isorhamnetin			5000	5	Immunotoxicity	0.58

					Aryl hydrocarbon Receptor (AhR) Aromatase Estrogen Receptor Alpha(ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) ATPase family AAA domain-containing protein 5 (ATAD5)	0.97 0.58 0.88 0.89 0.92 0.65
Isoangustone A	*Glcyrrhiza uralensis*	99.5/280.8	2500	5	Immunotoxicity Mitochondrial Membrane Potential (MMP)	0.93 0.73
Isocampneoside II	*Paulownia coreana*	9.72	5000	5	Immunotoxicity	0.99
Isoquercitrin	*Melastoma sanguineum*	4.33	5000	5	Immunotoxicity Phosphoprotein (Tumor Supressor) p53	0.66 0.50
Isovitexin	*Colocasia esculenta*	7.36	159	3	Mutagenicity	0.52
Isoliquiritigenin	*Glycyrrhiza uralensis*	3.4/27.5	3600	5	Immunotoxicity Estrogen Receptor Alpha(ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Supressor) p53 ATPase family AAA domain-containing protein 5 (ATAD5)	0.79 1.0 1.0 0.99 1.0 1.0
Irigenin	*Belamcanda chinensis*	2.42	2500	5	Immunotoxicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha(ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) ATPase family AAA domain-containing protein 5 (ATAD5)	0.98 0.84 0.69 0.60 0.86

						0.62
Jateorrhizine	*Tinospora cordifolia*	3.23	200	3	Immunotoxicity Mutagenicity Aryl hydrocarbon Receptor (AhR) Mitochondrial Membrane Potential (MMP)	0.98 0.52 0.50 0.73
Kakkalide	*Viola hondoensis*	(0.3µg/ml) 0.49	5000	5	Immunotoxicity Cytotoxicity	0.99 0.52
Kurarinone	*Sophora flavescens*	2.99/3.81	2000	4	Immunotoxicity Mitochondrial Membrane Potential (MMP)	0.99 0.60
Kurarinol	*Sophora flavescens*	2.13/4.39	2000	4	Immunotoxicity Aromatase Mitochondrial Membrane Potential (MMP)	0.99 0.52 0.61
Kushenol E	*Sophora flavescens*	7.74/2.09	2000	4	Immunotoxicity Mitochondrial Membrane Potential (MMP)	0.94 0.68
Loganin	*Corni fructus*	47.03±0.41 (RLAR) 308.5±61.8 (HRAR)	2000	4	Immunotoxicity	0.76
Lucidin	*Knoxia valerianoides*	3.35	5000	5	Immunotoxicity Mutagenicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha (ER) Mitochondrial Membrane Potential (MMP)	0.79 0.90 0.54 0.68 0.78
Luteolin	*Chrysanthemum indicum*	0.45	3919	5	Carcinogenicity Mutagenicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP)	0.68 0.51 0.91 0.87 0.95 1.0
Lucidumol A	*Ganoderma lucidum*	19.1	5010	6	Carcinogenicity Androgen Receptor (AR)	0.72 0.65

					Androgen Receptor Ligand Binding Domain (AR-LBD)	0.55
Lithospermic acid B	*Origanum vulgare L. ssp. hirtum*	96% at a dose of 100μM (RLAR)	25	2	Immunotoxicity Mutagenicity	 0.97 0.55
Licochalcone A	*Glycyrrhiza uralensis*	96.3/257.2	1000	4	Immunotoxicity Estrogen Receptor Alpha (ER) Mitochondrial Membrane Potential (MMP)	0.76 0.74 0.87
Methyl Corosolate	*Hippophae rhamnoides*	>20	1000	4	Carcinogenicity Immunotoxicity	0.56 0.98
Methyl lucidenate F	*Ganoderma lucidum*	76.8	4000	5	Androgen Receptor (AR) Androgen Receptor Ligand Binding Domain (AR-LBD) Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD)	0.89 0.76 0.61 0.74
Myrciaphenone B	*Myrcia multiflora*	29	2190	5	-----	----
Maesanin	*Maesa lanceolata*	1	2800	5	Immunotoxicity	0.99
Naringenin	*Paulownia coreana*	120.63	2000	4	Cytotoxicity Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Suppressor) p53 ATPase family AAA domain-containing protein 5 (ATAD5)	0.59 0.74 0.66 0.56 0.74 0.69 0.54
Nodakenin	*Angelica gigas*	(7.33μg/ml) 18.927	562	4	Immunotoxicity Mutagenicity Phosphoprotein (Tumor Suppressor) p53	0.51 0.52 0.52
Orientin	*Colocasia esculenta*	1.65	1213	4	Immunotoxicity Mutagenicity	0.52 0.52
Oxypaeoniflorin	*Paeonia suffruticosa*	>50	4000	5	-----	-----
P-coumaric acid	*Eleusine coracana*	(162.31 μg/ml) 988.73	2850	5	Carcinogenicity	0.50

Paeoniflorigenone	*Paeonia suffruticosa*	>50	2000	4	-----	----
Paeonol	*Paeonia suffruticosa*	>50	490	4	-----	-----
Paeonolide	*Paeonia suffruticosa*	>50	5000	5	Immunotoxicity	0.93
Palbinone	*Paeonia suffruticosa*	11.4	650	4	Carcinogenicity Immunotoxicity Androgen Receptor (AR) Androgen Receptor Ligand Binding Domain (AR-LBD)	0.63 0.95 0.75 0.62
Palmatine	*Tinospora cordifolia*	(3.8×10^{-5}M) 38	200	3	 Carcinogenicity Immunotoxicity Mutagenicity Cytotoxicity Aryl hydrocarbon Receptor(AhR) Mitochondrial Membrane Potential (MMP)	0.50 0.96 0.57 0.56 0.52 0.84
Pistafolin B	*Caesalpinia spinose*	(0.198mM) 198	2260	5	Immunotoxicity	0.70
Piceatannol	*Maackia amurensis*	>500	2400	5	Carcinogenicity Aryl hydrocarbon Receptor (AhR) Aromatase Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) Phosphoprotein (Tumor Suppressor) p53 ATPase family AAA domain-containing protein 5 (ATAD5)	0.52 0.68 0.60 1.0 0.90 0.95 1.0 1.0
Piperlongumine	*Piper chaba*	(160mM) 160000	1180	4	Immunotoxicity	0.99
Protocatechualdehyde	*Ganoderma applanatum*	(0.7μg/ml) 5.07	2195	5	Carcinogenicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Ligand Binding	0.77 0.54

					Domain (ER-LBD)	0.58
Protopine	*Glaucium aleppicum*	38.5	940	4	Carcinogenicity Immunotoxicity Mutagenicity	0.60 0.53 0.53
Puerariafuran	*Pueraria lobata*	22.34	138	3	Carcinogenicity Immunotoxicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) ATPase family AAA domain-containing protein 5 (ATAD5)	0.59 0.89 0.86 0.66 0.51 0.91 0.74
Quercetin	*Eleusine coracana*	14.8	159	3	Carcinogenicity Mutagenicity Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP)	0.68 0.51 0.91 0.87 0.95 1.0
Quercitrin	*Melastoma sanguineum*	0.16	5000	5	Carcinogenicity Immunotoxicity Aryl hydrocarbon Receptor (AhR)	0.50 0.97 0.55
Rhetsinine	*Euodia rutaecarpa*	24.1	1500	4	Mutagenicity	0.54
Rosmarinic acid	*Colocasia esculenta*	5.38	5000	5	Immunotoxicity	0.93
Rutin	*Nelumbo nucifera*	2.49±0.04 (RLAR)	5000	5	Immunotoxicity	0.98

Resveratrol	*Maackia amurensis*	117.6	1560	4	Aryl hydrocarbon Receptor (AhR) Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) ATPase family AAA domain-containing protein 5 (ATAD5)	1.0 1.0 1.0 1.0 1.0
Scopolin	*Artemisia montana*	128.15±1.72	5000	5	Immunotoxicity Mutagenicity	0.71 0.52
Scopoletin	*Magnolia fargesii*	22.5	3800	5	Immunotoxicity Mutagenicity Aryl hydrocarbon Receptor (AhR)	0.53 0.54 0.51
Scorparone	*Artemisia montana*	44.30±0.47 (RLAR)				
Semilicoisoflavone B	*Glycyrrhiza uralensis*	1.8/10.6	3850	5	Immunotoxicity Estrogen Receptor Alpha (ER) Mitochondrial Membrane Potential (MMP)	0.89 0.58 0.71
Syringic acid	*Eleusine coracana*	(172.1µg/ml) 868.44	1700	4	-----	----
Trans-anethole	*Foeniculum vulgare*	(3.8 µg/ml) 25.64	150	3	Carcinogenicity	0.57
Trans-ferulic acid	*Maackia amurensis*	>500	1772	4	Immunotoxicity	0.91
Tectorigenin	*Belamcanda chinensis*	1.12 (RLAR)	2500	5	Immunotoxicity Aryl hydrocarbon Receptor (AhR) Aromatase Estrogen Receptor Alpha (ER) Estrogen Receptor Ligand Binding Domain (ER-LBD) Mitochondrial Membrane Potential (MMP) ATPase family AAA domain-containing protein 5 (ATAD5)	0.71 0.97 0.58 0.88 0.89 0.92 0.65

Tingenin B	*Salacia chinensis*	7	2000	4	Carcinogenicity Immunotoxicity	0.50 0.99
Tiliroside	*Magnolia fargesii*	14.9	5000	5	Immunotoxicity	0.97
Ursolic acid	*Vaccinium vitis-idaea*	>20	2000	4	Hepatotoxicity Carcinogenicity Immunotoxicity Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE) Heat shock factor response element (HSE)	0.52 0.57 0.95 0.70 0.70
Verbascoside	*Paulownia coreana*	2.67	5000	5	Immunotoxicity	0.99
7-O-galloyl-D-sedoheptulose	*Corni fructus*	296.1±0.89 (RLAR) 592.0±23.4 (HRAR)	3700	5	----	----
7-O-methyl luteone	*Glycyrrhiza uralensis*	28.5/76.5				
(-)-Epicatechin	*Green Tea*	79 (RLAR)	10000	6	Mitochondrial Membrane Potential (MMP)	0.55
(+)-trans-decursinol	*Angelica decursiva*	1.03±0.02 (HRAR)	832	4	---------	-----
2,6-bis(3,4-dihydroxy benzylidene) cyclohexanone	*Curcuma longa*	2.9	2300	5	Carcinogenicity Immunotoxicity Nuclear factor(erythroid-derived 2)-like2/antioxidant responsive element (nrf2/ARE) Heat shock factor response element (HSE) Mitochondrial Membrane Potential (MMP)	0.60 0.58 0.53 0.53 0.90

2,5-bis(3,4-dihydroxy benzylidene) cyclopentanone	*Curcuma longa*	2.6	2560	5	Carcinogenicity Immunotoxicity Mitochondrial Membrane Potential (MMP)	0.62 0.66 0.90
2-(4-hydroxy-3-methoxy phenyl) ethanoic acid	*Zingiber officinale Roscoe*	18.5±1.1	1123	4	----	-----

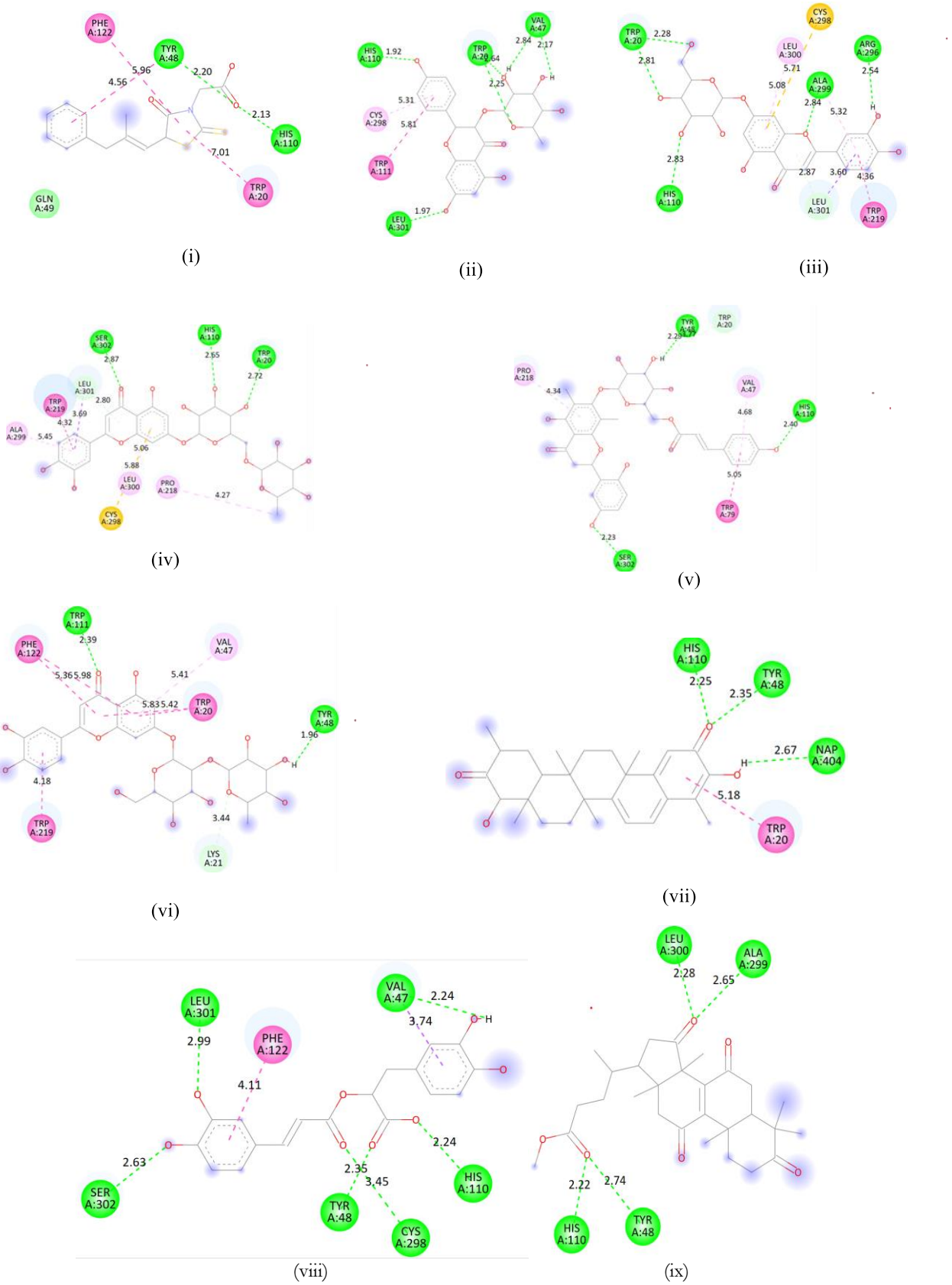


Figure S1: 2D interaction of (i) Epalrestat (ii) Engeletin (iii) Luteolin-7-O-glucoside (iv) Luteolin-7-rutinoside (v) Myrciacitrin IV (vi) Scolymoside (vii) Tingenin B with 4JIR (viii) Rosmarinic acid (ix) Methyl Lucidenate F

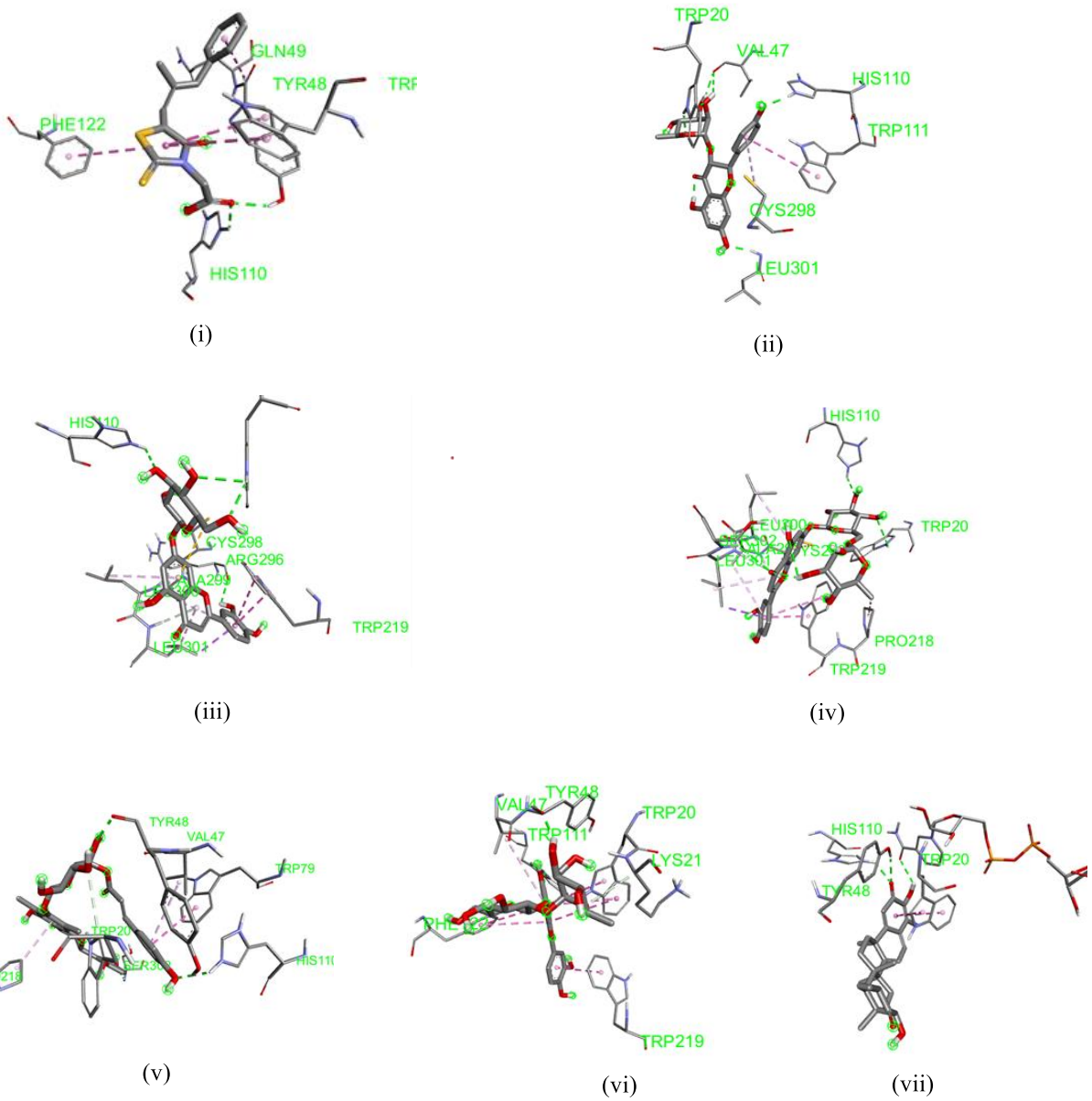
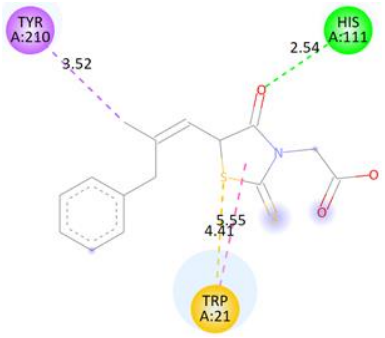
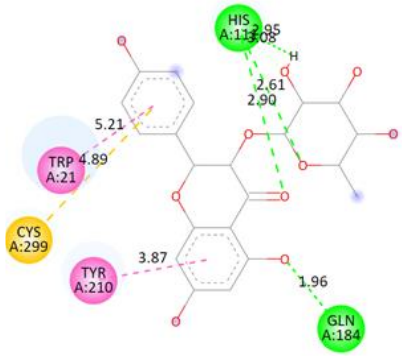


Figure S2: 3D interaction of (i) Epalrestat (ii) Engeletin (iii) Luteolin-7-O-glucoside (iv) Luteolin-7-rutinoside (v) Myrciacitrin IV (vi) Scolymoside (vii) Tingenin B with 4JIR.



(i)



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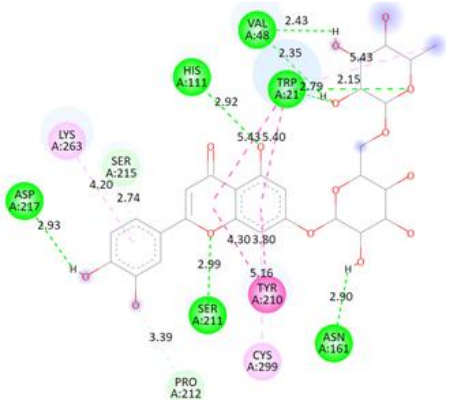

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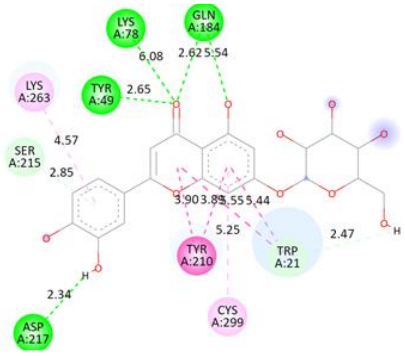

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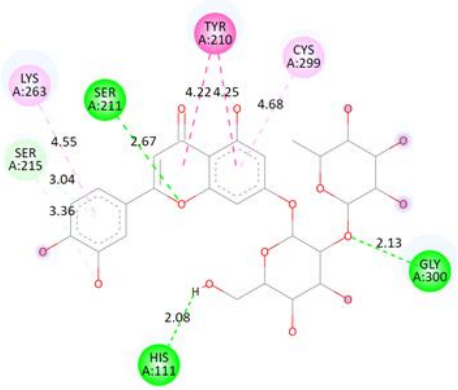

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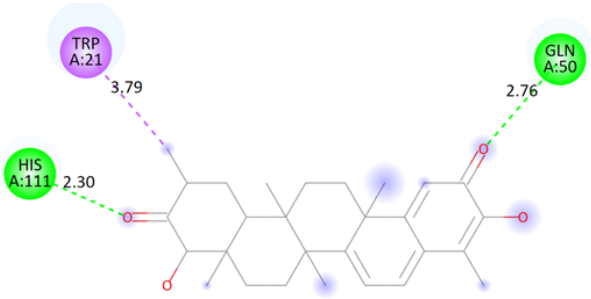

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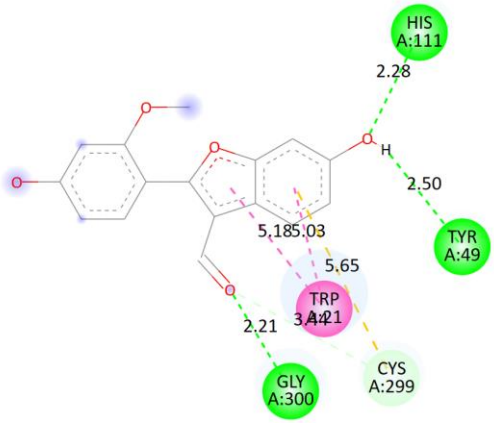

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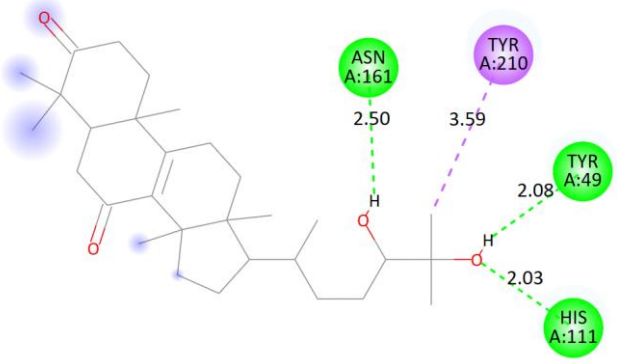

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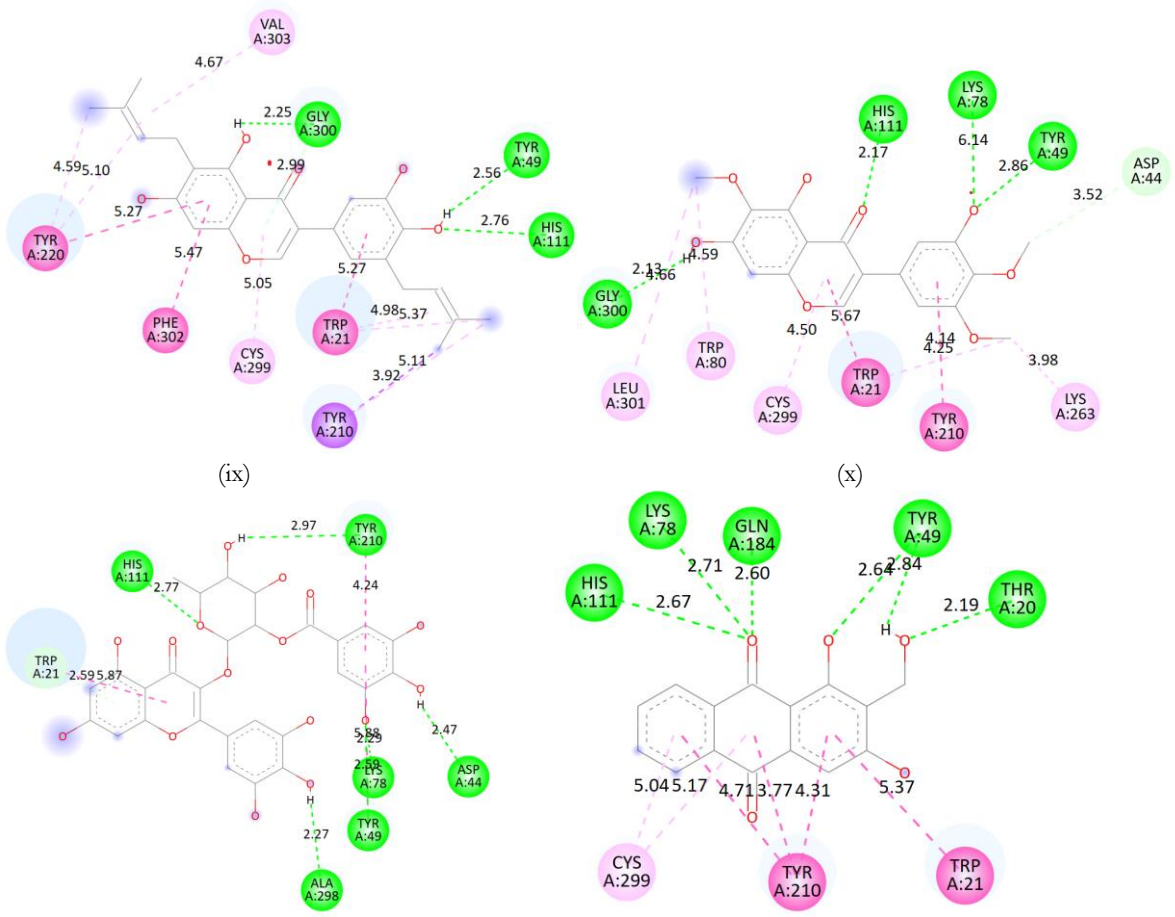

Figure S3: 2D interaction of (i) Epalrestat (ii) Engeletin (iii) Luteolin-7-O-glucoside (iv) Luteolin-7-rutinoside (v) Scolymoside (vi) Tingenin B (vii) Puerariafuran (viii) Lucidumol A (ix) Isoangustone A (x) Irigenin (xi) Desmanthin-I (xii) Lucidin with 3O3R.

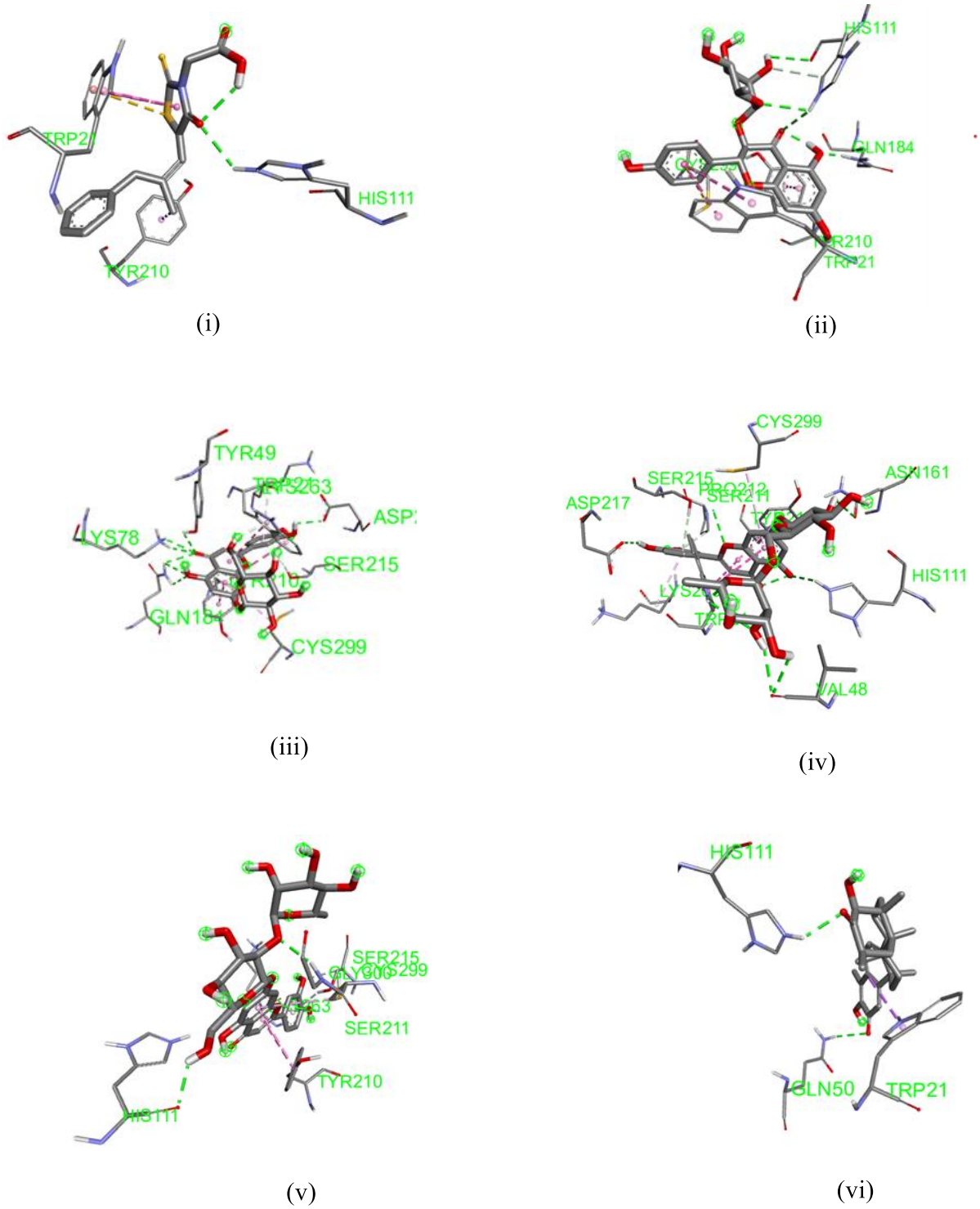

Figure S4: 3D interaction of (i) Epalrestat (ii) Engeletin (iii) Luteolin-7-O-glucoside (iv) Luteolin7-rutinoside (v) Scolymoside (vi) Tingenin B with 3O3R