Supplementary Information

Interaction of *Jania rubens* Polyphenolic Extract as an Antidiabetic Agent with α-Amylase, Lipase, and Trypsin: In Vitro Evaluations and In Silico Studies

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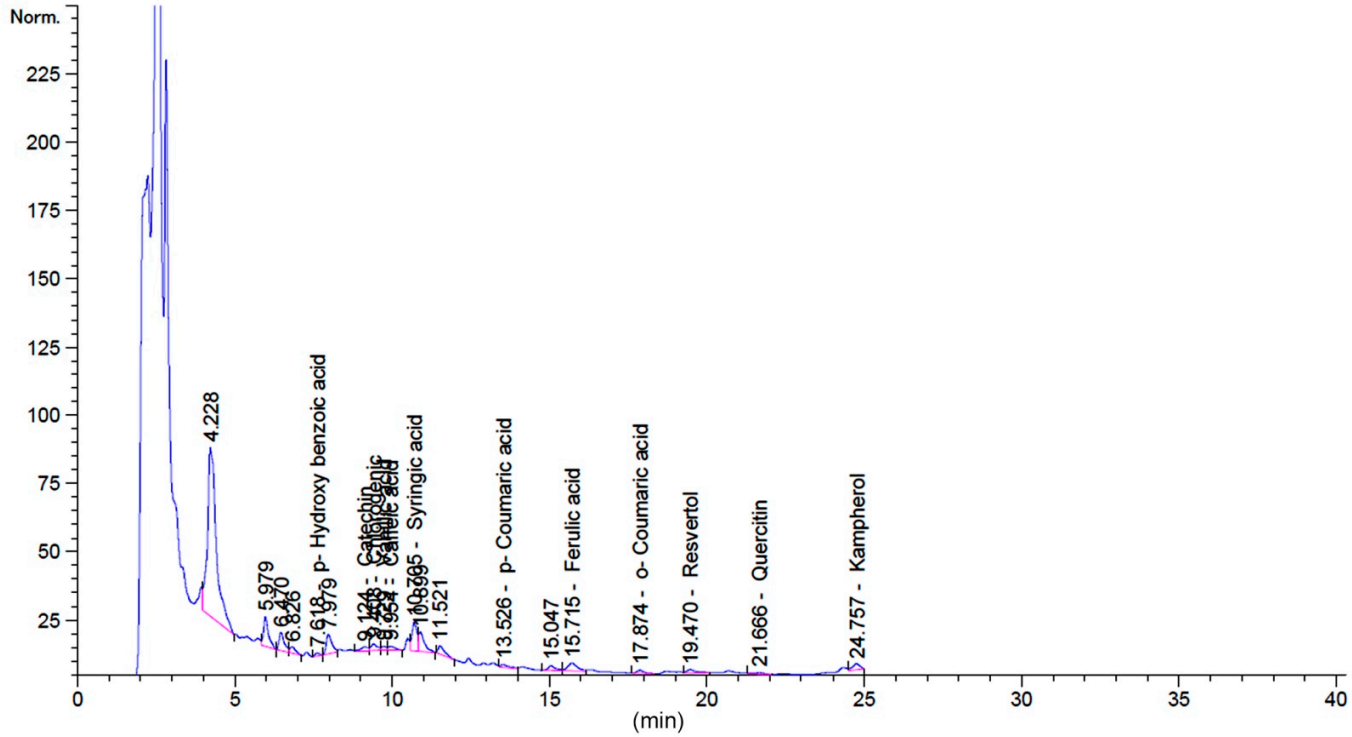
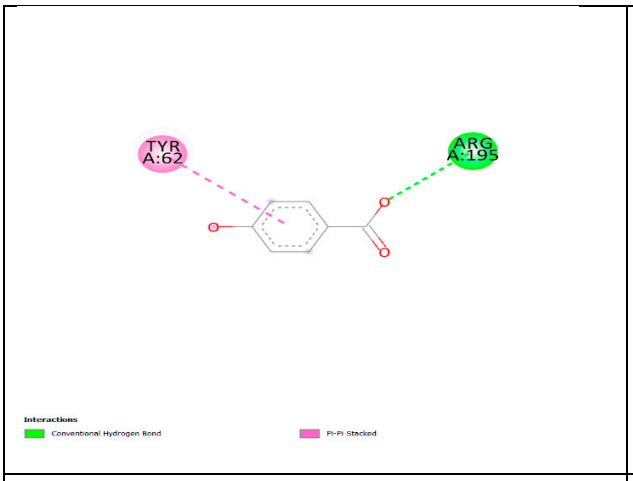
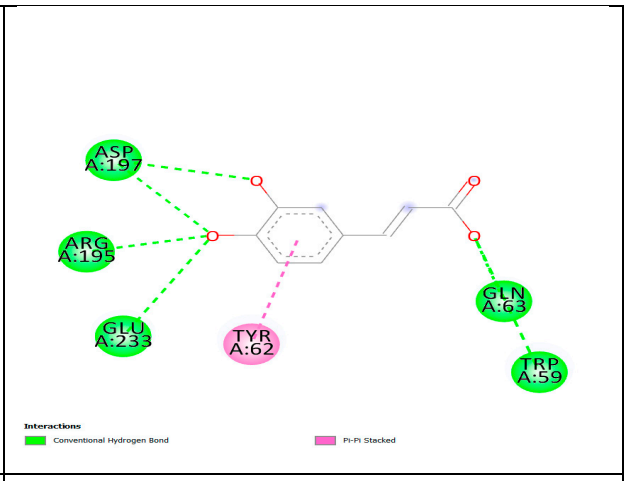
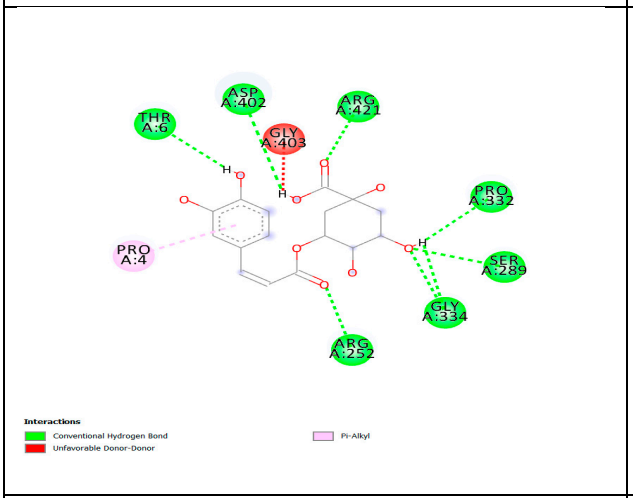
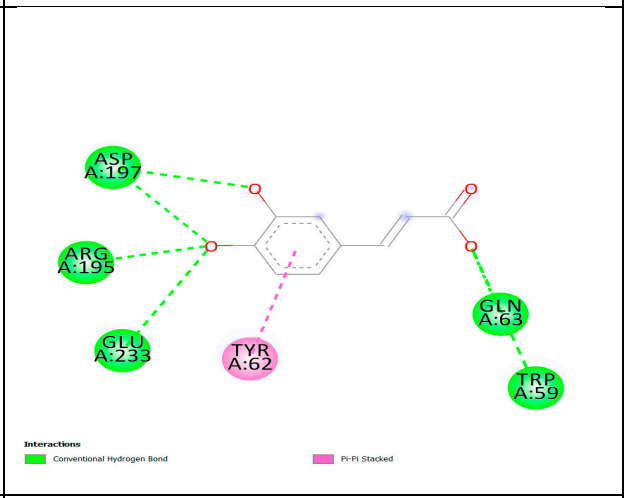


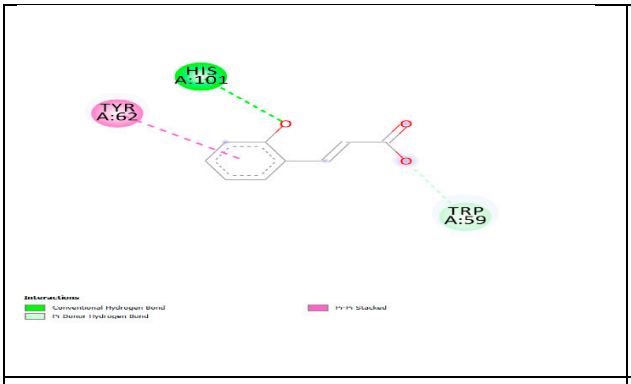
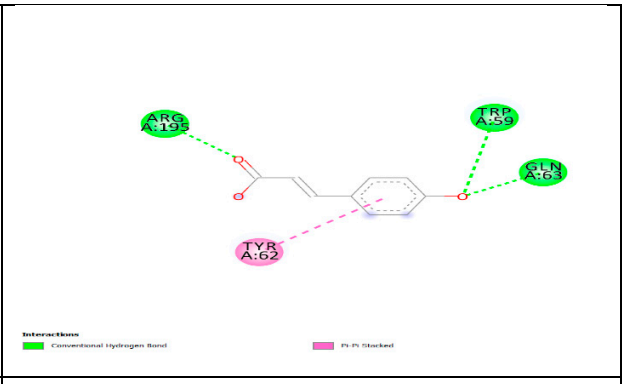
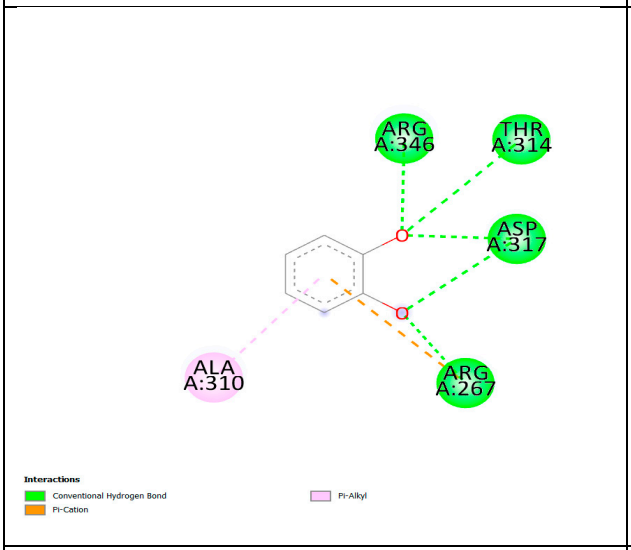
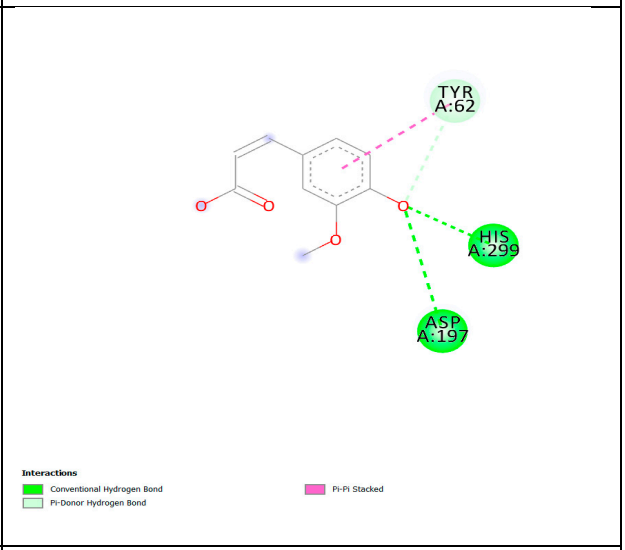
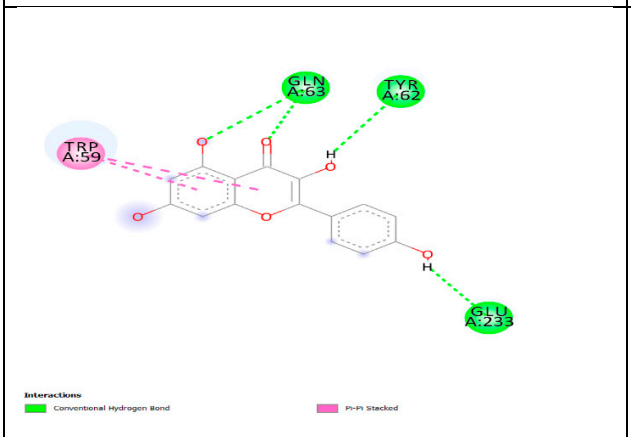
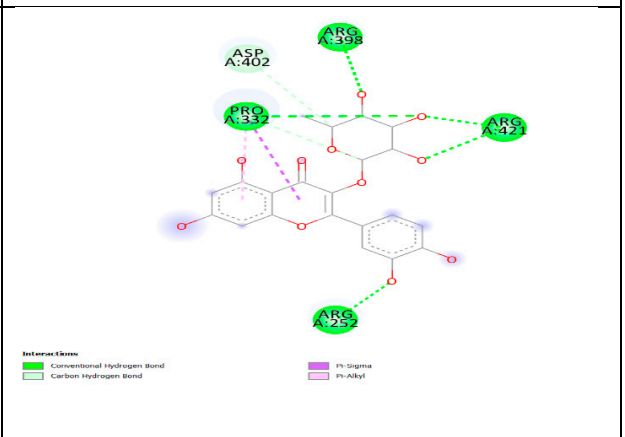
Figure S1. HPLC chromatogram for the JRPE shows different polyphenolic compounds (phenolic and flavonoids).

Table S1. The docking affinity scores of the different polyphenolics' compounds in the JRPE.

Compounds	α-Amylase Affinity	a.a residue	Lipase Affinity	**a.a residue**	**Trypsin Affinity**	**a.a residue**
P- Hydroxybenzoic acid	-5.3	TYR62 ,ARG195	-4.9	SER195 .CYS220 .GLY226	-5	SER195, CYS220 ,GLY226
Caffeic acid	-5.7	TRP59 ,TYR62 ,GLN63 ,ARG195 ,ASP197 ,GLU233	-4.7	CYS42 ,HIS57 ,TYR59 ,GLY193	-4.7	CYS42, HIS57 ,TYR59 ,GLY193
Catechin	-4.5	ARG267 ,ALA310 ,THR314 ,ASP317 ,ARG346	-4.3	SER195	-4.3	SER195
Chlorogenic	-8	PRO4 ,THR6 ,ARG252 ,SER289 ,PRO332 ,GLY334 ,ASP402 .GLY403 ,ARG421	-7.1	LEU18 ,HIS30 ,ILE33 ,SER35 ,SER37 ,TYR55 ,ILE79 ,THR80	-7.1	PHE41 ,TYR151 ,GLY193 SER195 ,GLY219
Ferulic acid	-6.1	TYR62 .ASP197 ,HIS299	-5.3	HIS57 ,SER190 ,CYS191 SER195 ,CYS220	-5.2	HIS57 ,SER190 ,CYS191 ,SER195 ,CYS220
Kaempferol	-8.4	TRP59, TYR62 ,GLN63 .GLU233	-7.1	HIS57 ,ASP189 ,SER190 ,GLN192 ,GLY193 ,TRP215 .GLY216	-7.2	HIS57 ,ASP189 ,SER190 ,GLN192 ,GLY193 ,TRP215 ,GLY216
o-Coumaric acid	-5.8	TRP59, TYR62 .HIS101	-4.7	TYR59 ,THR90	-4.6	TYR59 ,THR90
p-Coumaric acid	-5.7	TRP59, TYR62 ,GLN63 ,ARG195	-4.8	ASN34 ,ARG62 ,GLN64 ,ARG66	-4.3	ASN34 ,ARG62, GLN64 ,ARG66
Quercetin	-8.8	ARG252 ,PRO332 ,ARG398 ,ASP402 ,ARG421	-7.4	HIS57 ,TYR151 ,CYS191 ,GLY193 ,ASP194 ,SER195	-7.2	HIS57 ,TYR151 ,CYS191 ,GLY193 ,ASP194 ,SER195
Resveratrol	-7.4	TYR62 ,THR163 ,ASP197 ,HIS299	-6	HIS57 ,LEU99 ,SER214 ,TRP215 ,GLY216	-5.8	HIS57 ,LEU99 ,SER214 ,TRP215 ,GLY216
Syringic acid	-5.8	ARG252 SER289,GLY334 ,PHE335 ,ARG398	-4.9	SER190 ,CYS191 ,GLY193 ,SER195 ,GLY216 ,GLY219	-5.5	SER190 ,CYS191,GLY193 ,SER195 ,GLY216 ,GLY219
Vanillic acid	-5.4	ARG252 ,SER289 ,ASP290 ,PRO332 ,GLY334 ,ARG398	-4.8	LYS60 ,SER61 ,ARG62	-4.1	LYS60 ,SER61 ,ARG62

Table S2. Affinity scores for docking analysis of α-amylase (PDB ID: 4W93) using twelve polyphenolic compounds identified from JRPE.

	
***P*-Hydroxybenzoic acid**	**Caffeic acid**
	
Chlorogenic	**Vanillic acid**

	
***O*-Coumaric acid**	***P*-Coumaric acid**
	
Catechin	**Ferulic acid**
	
Kaempferol	**Quercetin**

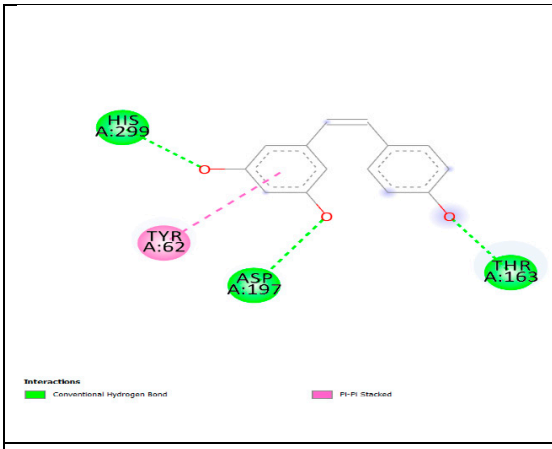
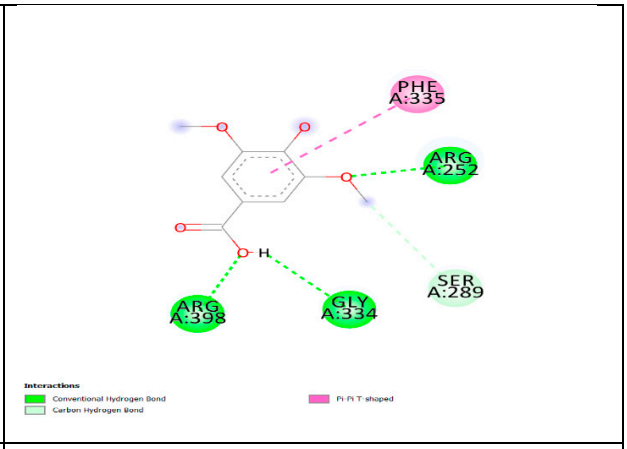
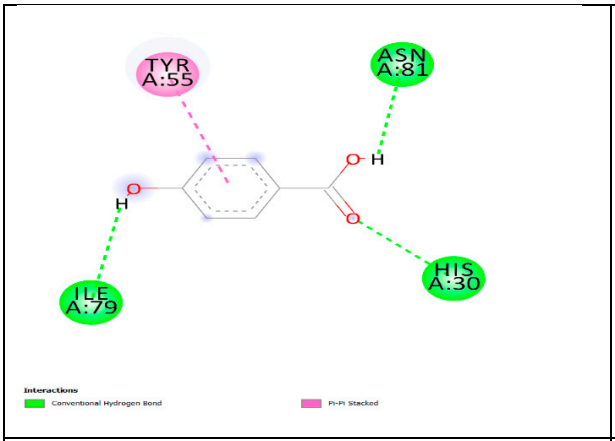
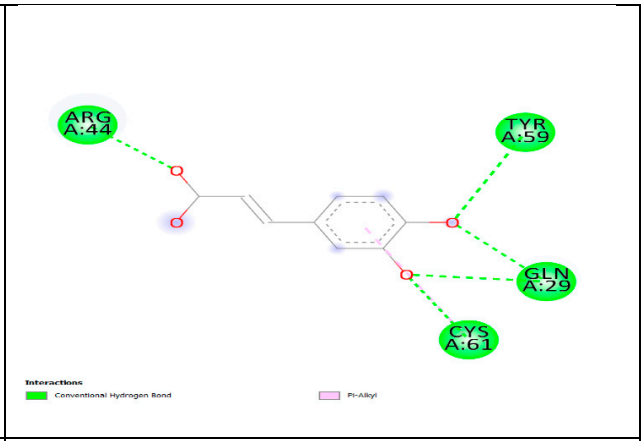
	
Resveratrol	**Syringic acid**

Table S3. Affinity scores for docking analysis of lipase (PDB ID: 1LPB) using twelve polyphenolic compounds identified from JRPE.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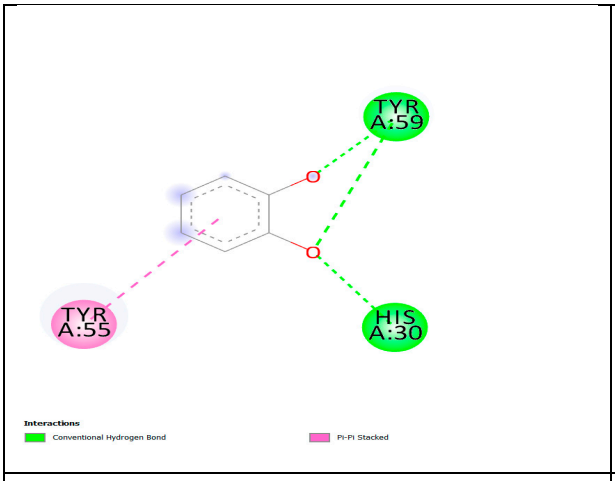
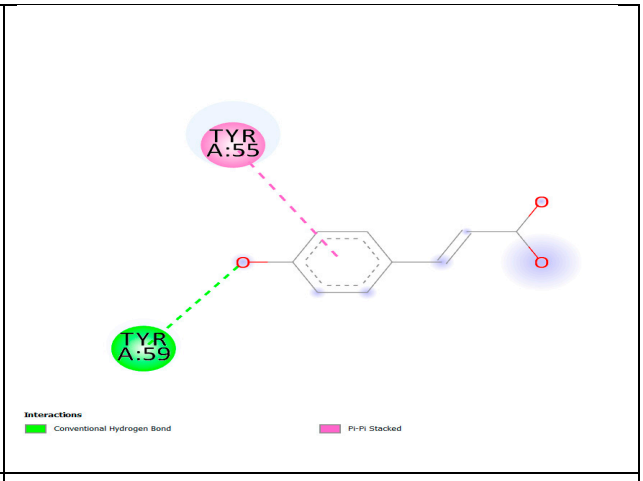
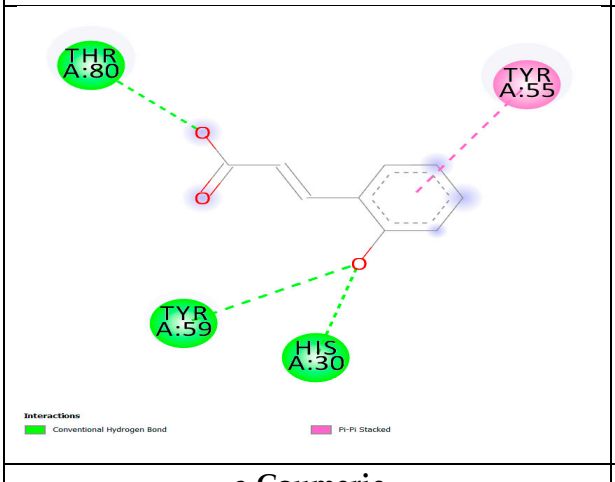
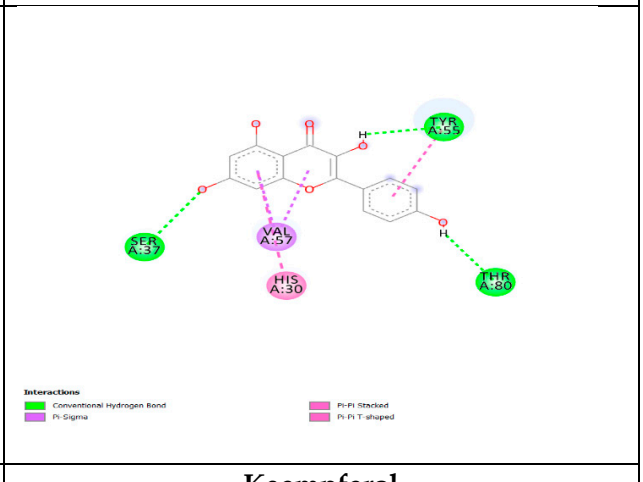
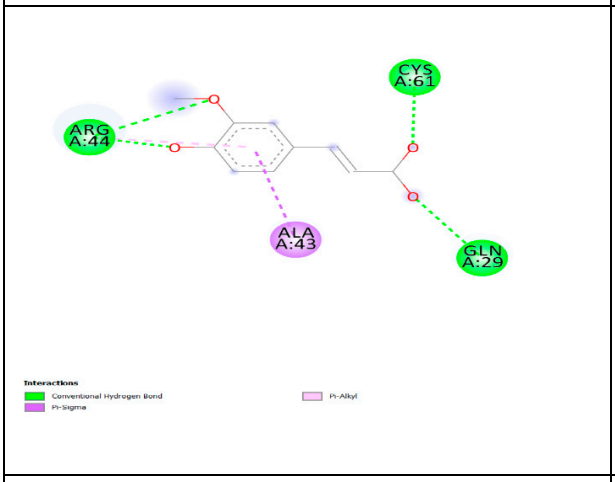
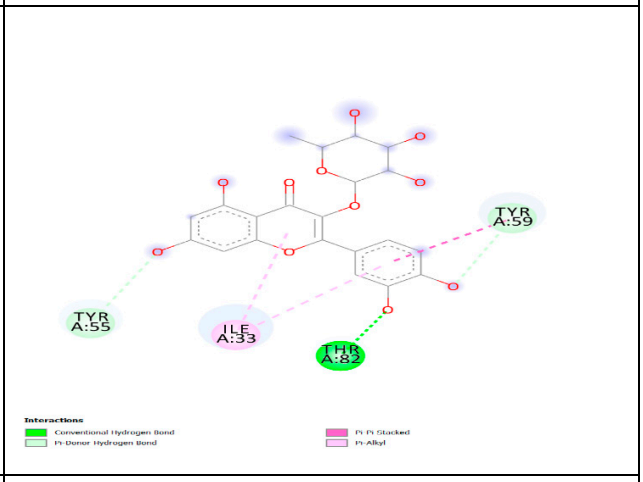
	
Catechin	***P*-coumaric acid**
	
***o*-Coumaric**	**Kaempferol**
	
Ferulic acid	**Quercetin**

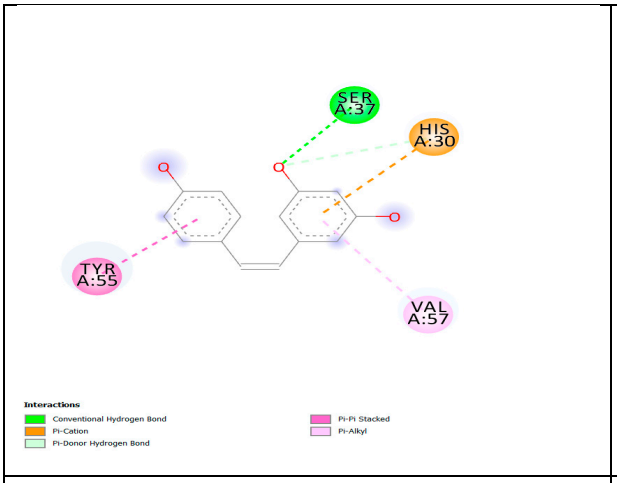
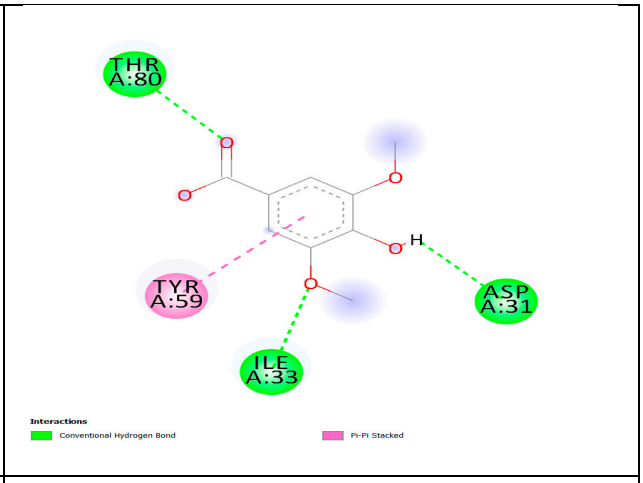
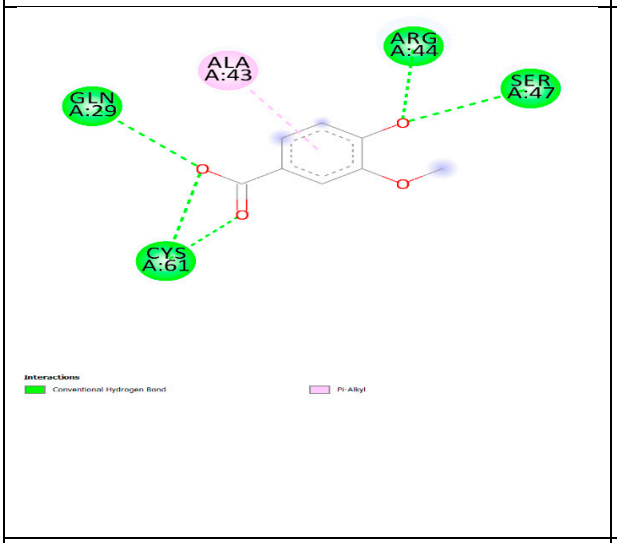
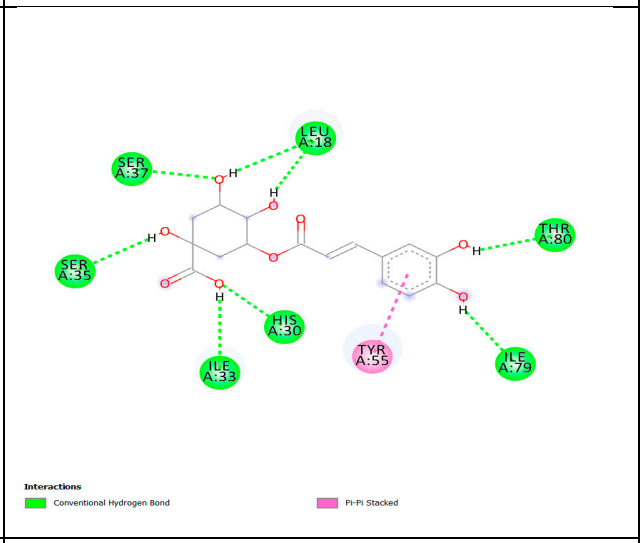
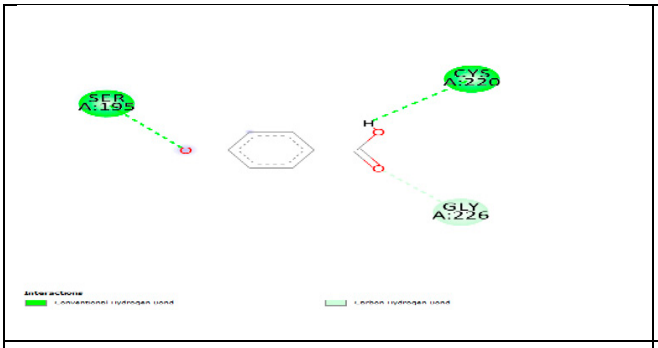
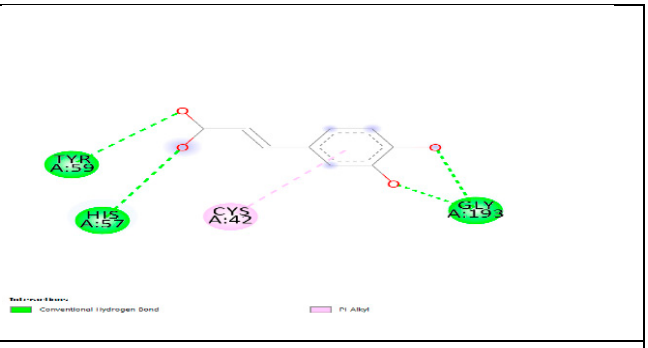
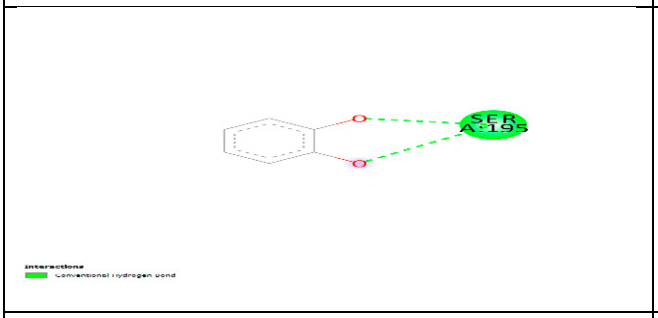
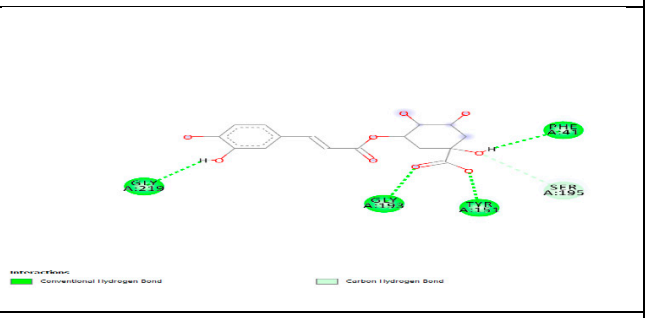
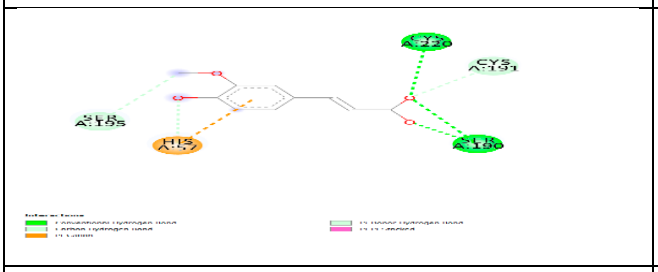
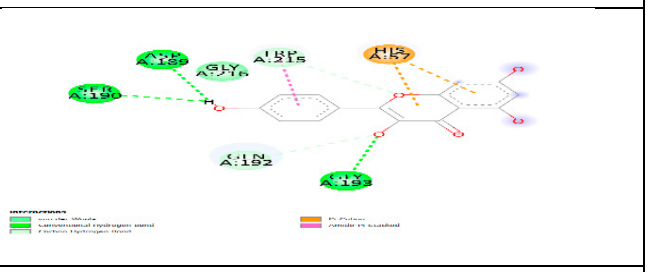
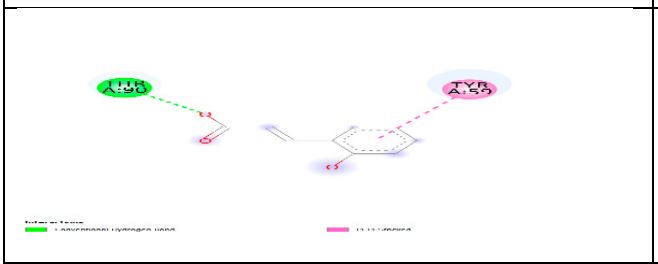
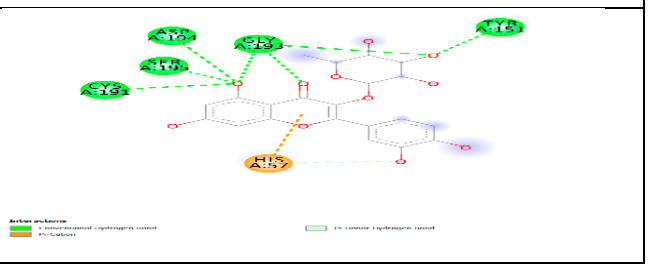
	
Resveratrol	**Syringic acid**
	
Vanillic acid	**Chlorogenic acid**

Table S4. Affinity scores for docking analysis of trypsin (PDB ID: 4DOQ) using twelve polyphenolic compounds identified from JRPE.

	
***p*-Hydroxybenzoic acid**	**Caffeic acid**
	
Catechin	**Chlorogenic acid**
	
Ferulic	**Kaempferol**
	
***o*-coumaric acid**	**Quercetin**

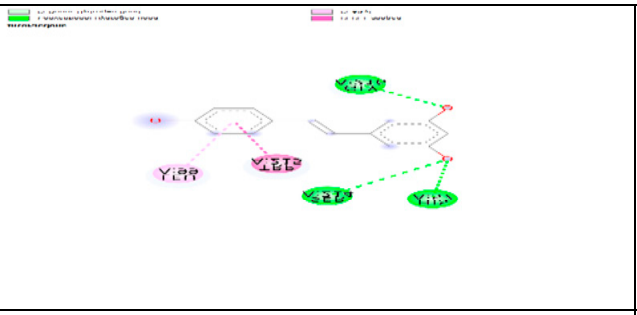
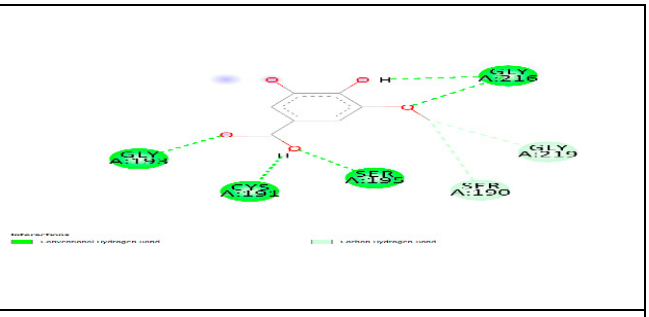
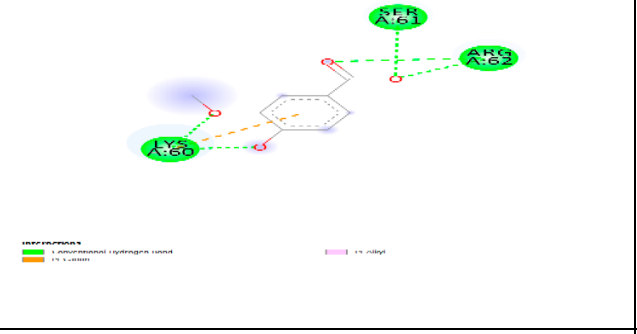
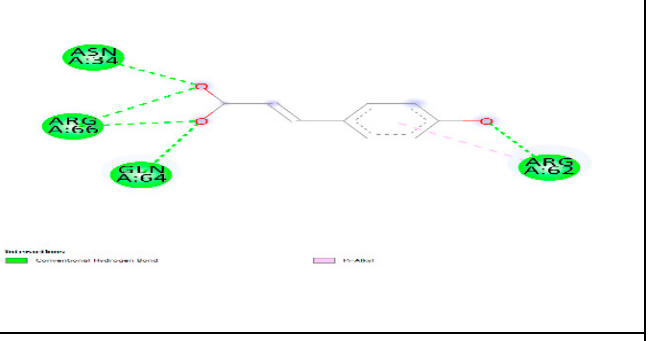
	
Resveratrol	**Syringic acid**
	
Vanillic acid	***p*-Coumaric acid**

Table S5. Pharmacodynamics and pharmacokinetics analysis of twelve polyphenolic compounds identified from JRPE.

Compounds	Pharmacokinetics	Medicinal Chemistry	Drug likeness	Physicochemical Properties	Lipophilicity	Water Solubility
Resveratrol	GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor Yes CYP2C19 inhibitor No CYP2C9 inhibitor Yes CYP2D6 inhibitor No CYP3A4 inhibitor Yes Log Kp (skin permeation) -5.47 cm/s	PAINS 0 alert Brenk 1 alert: stilbene Leadlikeness No; 1 violation: MW<250 Synthetic accessibility 2.02	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes Muegge Yes Bioavailability Score 0.55	Formula C14H12O3 Molecular weight 228.24 g/mol Num. heavy atoms 17 Num. arom. heavy atoms 12 Fraction Csp3 0.00 Num. rotatable bonds 2 Num. H-bond acceptors 3 Num. H-bond donors 3 Molar Refractivity 67.88 TPSA 60.69 Å²	Log Po/w (iLOGP) 1.71 Log Po/w (XLOGP3) 3.13 Log Po/w (WLOGP) 2.76 Log Po/w (MLOGP) 2.26 Log Po/w (SILICOS-IT) 2.57 Consensus Log Po/w 2.48	Log S (ESOL) -3.62 Solubility 5.51e-02 mg/ml ; 2.41e-04 mol/l Class Soluble Log S (Ali) -4.07 Solubility 1.93e-02 mg/ml ; 8.44e-05 mol/l Class Moderately soluble Log S (SILICOS-IT) -3.29 Solubility 1.18e-01 mg/ml ; 5.16e-04 mol/l Class Soluble
P-Coumarate	GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -6.26 cm/s	PAINS 0 alert Brenk 1 alert: michael_acceptor_1 Leadlikeness No; 1 violation: MW<250 Synthetic accessibility 1.61	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes Muegge No; 1 violation: MW<200 Bioavailability Score 0.85	Formula C9H8O3 Molecular weight 164.16 g/mol Num. heavy atoms 12 Num. arom. heavy atoms 6 Fraction Csp3 0.00 Num. rotatable bonds 2 Num. H-bond acceptors 3 Num. H-bond donors 2 Molar Refractivity 45.13 TPSA 57.53 Å²	Log Po/w (iLOGP) 0.95 Log Po/w (XLOGP3) 1.46 Log Po/w (WLOGP) 1.38 Log Po/w (MLOGP) 1.28 Log Po/w (SILICOS-IT) 1.22 Consensus Log Po/w 1.26	Log S (ESOL) -2.02 Solubility 1.58e+00 mg/ml ; 9.65e-03 mol/l Class Soluble Log S (Ali) -2.27 Solubility 8.73e-01 mg/ml ; 5.32e-03 mol/l Class Soluble Log S (SILICOS-IT) -1.28 Solubility 8.67e+00 mg/ml ; 5.28e-02 mol/l Class Soluble
Caffeic Acid	GI absorption High	PAINS 1 alert:	Lipinski Yes; 0 violation	Formula C9H8O4	Log Po/w (iLOGP) 0.97	Log S (ESOL) -1.89

	BBB permeant No P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -6.58 cm/s	catechol_A Brenk 2 alerts: catechol, michael_acceptor_1 Lead likeness No; 1 violation: MW<250 Synthetic accessibility 1.81	Ghose Yes Veber Yes Egan Yes Muegge No; 1 violation: MW<200 Bioavailability Score 0.56	Molecular weight 180.16 g/mol Num. heavy atoms 13 Num. arom. heavy atoms 6 Fraction Csp3 0.00 Num. rotatable bonds 2 Num. H-bond acceptors 4 Num. H-bond donors 3 Molar Refractivity 47.16 TPSA 77.76 Å²	Log Po/w (XLOGP3) 1.15 Log Po/w (WLOGP) 1.09 Log Po/w (MLOGP) 0.70 Log Po/w (SILICOS-IT) 0.75 Consensus Log Po/w 0.93	Solubility 2.32e+00 mg/ml ; 1.29e-02 mol/l Class Very soluble Log S (Ali) -2.38 Solubility 7.55e-01 mg/ml ; 4.19e-03 mol/l Class Soluble Log S (SILICOS-IT) -0.71 Solubility 3.51e+01 mg/ml ; 1.95e-01 mol/l Class Soluble
Catechin	GI absorption High BBB permeant No P-gp substrate Yes CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -7.82 cm/s	PAINS 1 alert: catechol_A Brenk 1 alert: catechol Leadlikeness Yes Synthetic accessibility 3.50	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes Muegge Yes Bioavailability Score 0.55	Formula C15H14O6 Molecular weight 290.27 g/mol Num. heavy atoms 21 Num. arom. heavy atoms 12 Fraction Csp3 0.20 Num. rotatable bonds 1 Num. H-bond acceptors 6 Num. H-bond donors 5 Molar Refractivity 74.33 TPSA 110.38 Å²	Log Po/w (iLOGP) 1.47 Log Po/w (XLOGP3) 0.36 Log Po/w (WLOGP) 1.22 Log Po/w (MLOGP) 0.24 Log Po/w (SILICOS-IT) 0.98 Consensus Log Po/w 0.85	Log S (ESOL) -2.22 Solubility 1.74e+00 mg/ml ; 5.98e-03 mol/l Class Soluble Log S (Ali) -2.24 Solubility 1.66e+00 mg/ml ; 5.72e-03 mol/l Class Soluble Log S (SILICOS-IT) -2.14 Solubility 2.09e+00 mg/ml ; 7.19e-03 mol/l Class Soluble
Ferulate	GI absorption High BBB permeant Yes P-gp substrate No	PAINS 0 alert Brenk 1 alert: michael_acceptor_1 Leadlikeness No; 1 violation: MW<250	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes	Formula C10H10O4 Molecular weight 194.18 g/mol Num. heavy atoms 14 Num. arom. heavy atoms	Log Po/w (iLOGP) 1.62 Log Po/w (XLOGP3) 1.51 Log Po/w (WLOGP) 1.39 Log Po/w (MLOGP) 1.00	Log S (ESOL) -2.11 Solubility 1.49e+00 mg/ml ; 7.68e-03 mol/l Class Soluble

	CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -6.41 cm/s	Synthetic accessibility 1.93	Muegge No; 1 violation: MW<200 Bioavailability Score 0.85	6 Fraction Csp3 0.10 Num. rotatable bonds 3 Num. H-bond acceptors 4 Num. H-bond donors 2 Molar Refractivity 51.63 TPSA 66.76 Å²	Log Po/w (SILICOS-IT) SILICOS-IT: Hybrid fragmental/topological method calculated by FILTER-IT program, version 1.0.2, courtesy of SILICOS-IT, http://www.silicos-it.com 1.26 Consensus Log Po/w 1.36	Log S (Ali) -2.52 Solubility 5.86e-01 mg/ml ; 3.02e-03 mol/l Class Soluble Log S (SILICOS-IT) -1.42 Solubility 7.43e+00 mg/ml ; 3.83e-02 mol/l Class Soluble
Kaempferol	GI absorption High BBB permeant No P-gp substrate No CYP1A2 inhibitor Yes CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor Yes CYP3A4 inhibitor Yes Log Kp (skin permeation) -6.70 cm/s	PAINS 0 alert Brenk 0 alert Leadlikeness Yes Synthetic accessibility 3.14	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes Muegge Yes Bioavailability Score 0.55	Formula C15H10O6 Molecular weight 286.24 g/mol Num. heavy atoms 21 Num. arom. heavy atoms 16 Fraction Csp3 0.00 Num. rotatable bonds 1 Num. H-bond acceptors 6 Num. H-bond donors 4 Molar Refractivity 76.01 TPSA 111.13 Å²	Log Po/w (iLOGP) 1.70 Log Po/w (XLOGP3) 1.90 Log Po/w (WLOGP) 2.28 Log Po/w (MLOGP) -0.03 Log Po/w (SILICOS-IT) 2.03 Consensus Log Po/w 1.58	Log S (ESOL) -3.31 Solubility 1.40e-01 mg/ml ; 4.90e-04 mol/l Class Soluble Log S (Ali) -3.86 Solubility 3.98e-02 mg/ml ; 1.39e-04 mol/l Class Soluble Log S (SILICOS-IT) -3.82 Solubility 4.29e-02 mg/ml ; 1.50e-04 mol/l Class Soluble
Quercetin	GI absorption Low BBB permeant No P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No	PAINS 1 alert: catechol_A Brenk 1 alert: catechol Leadlikeness No; 1 violation: MW>350 Synthetic accessibility 5.28	Lipinski No; 2 violations: NorO>10, NHorOH>5 Ghose Yes Veber No; 1 violation: TPSA>140 Egan No; 1 violation: TPSA>131.6 Muegge No; 3 violations:	Formula C21H20O11 Molecular weight 448.38 g/mol Num. heavy atoms 32 Num. arom. heavy atoms 16 Fraction Csp3 0.29	Log Po/w (iLOGP) 1.60 Log Po/w (XLOGP3) 0.86 Log Po/w (WLOGP) 0.49 Log Po/w (MLOGP) -1.84 Log Po/w (SILICOS-IT) 0.01	Log S (ESOL) -3.33 Solubility 2.08e-01 mg/ml ; 4.64e-04 mol/l Class Soluble Log S (Ali) -4.44 Solubility 1.63e-02 mg/ml ; 3.63e-05 mol/l

	CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -8.42 cm/s		TPSA>150, H-acc>10, H-don>5 Bioavailability Score 0.17	Num. rotatable bonds 3 Num. H-bond acceptors 11 Num. H-bond donors 7 Molar Refractivity 109.00 TPSA 190.28 Å²	Consensus Log Po/w 0.22	Class Moderately soluble Log S (SILICOS-IT) -2.08 Solubility 3.69e+00 mg/ml ; 8.22e-03 mol/l Class Soluble
Chlorogenic Acid	GI absorption Low BBB permeant No P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -8.62 cm/s	PAINS 1 alert: catechol_A Brenk 3 alerts: catechol, michael_acceptor_1, more_than_2_esters Leadlikeness No; 1 violation: MW>350 Synthetic accessibility 4.27	Lipinski Yes; 0 violation Ghose No; 1 violation: WLOGP<-0.4 Veber No; 1 violation: TPSA>140 Egan No; 1 violation: TPSA>131.6 Muegge No; 1 violation: TPSA>150 Bioavailability Score 0.55	Formula C17H20O9 Molecular weight 368.34 g/mol Num. heavy atoms 26 Num. arom. heavy atoms 6 Fraction Csp3 0.41 Num. rotatable bonds 6 Num. H-bond acceptors 9 Num. H-bond donors 5 Molar Refractivity 87.82 TPSA 153.75 Å²	Log Po/w (iLOGP) 1.64 Log Po/w (XLOGP3) -0.10 Log Po/w (WLOGP) -0.67 Log Po/w (MLOGP) -0.81 Log Po/w (SILICOS-IT) -0.07 Consensus Log Po/w -0.00	Log S (ESOL) -1.84 Solubility 5.38e+00 mg/ml ; 1.46e-02 mol/l Class Very soluble Log S (Ali) -2.68 Solubility 7.76e-01 mg/ml ; 2.11e-03 mol/l Class Soluble Log S (SILICOS-IT) -0.29 Solubility 1.89e+02 mg/ml ; 5.13e-01 mol/l Class Soluble
4-Hydroxybenzoic acid	GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No	PAINS 0 alert Brenk 0 alert Leadlikeness No; 1 violation: MW<250 Synthetic accessibility 1.00	Lipinski Yes; 0 violation Ghose No; 3 violations: MW<160, MR<40, #atoms<20 Veber Yes Egan Yes Muegge No; 1 violation: MW<200 Bioavailability Score 0.85	Formula C7H6O3 Molecular weight 138.12 g/mol Num. heavy atoms 10 Num. arom. heavy atoms 6 Fraction Csp3 0.00 Num. rotatable bonds 1 Num. H-bond acceptors	Log Po/w (iLOGP) 0.85 Log Po/w (XLOGP3) 1.58 Log Po/w (WLOGP) 1.09 Log Po/w (MLOGP) 0.99 Log Po/w (SILICOS-IT) 0.74 Consensus Log Po/w 1.05	Log S (ESOL) -2.07 Solubility 1.18e+00 mg/ml ; 8.52e-03 mol/l Class Soluble Log S (Ali) -2.40 Solubility 5.51e-01 mg/ml ; 3.99e-03 mol/l Class Soluble

	Log Kp (skin permeation) -6.02 cm/s			3 Num. H-bond donors 2 Molar Refractivity 35.42 TPSA 57.53 Å²		Log S (SILICOS-IT) -1.17 Solubility 9.40e+00 mg/ml ; 6.81e-02 mol/lClass Soluble
o-Coumaric acid	GI absorption High BBB permeant Yes P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -5.86 cm/s	PAINS 0 alert Brenk 1 alert: michael_acceptor_1 Leadlikeness No; 1 violation: MW<250 Synthetic accessibility 1.85	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes Muegge No; 1 violation: MW<200 Bioavailability Score 0.85	Formula C9H8O3 Molecular weight 164.16 g/mol Num. heavy atoms 12 Num. arom. heavy atoms 6 Fraction Csp3 0.00 Num. rotatable bonds 2 Num. H-bond acceptors 3 Num. H-bond donors 2 Molar Refractivity 45.13 TPSA 57.53 Å²	Log Po/w (iLOGP) 1.09 Log Po/w (XLOGP3) 2.03 Log Po/w (WLOGP) 1.38 Log Po/w (MLOGP) 1.28 Log Po/w (SILICOS-IT) 1.22 Consensus Log Po/w 1.40	Log S (ESOL) -2.37 Solubility 6.93e-01 mg/ml ; 4.22e-03 mol/l Class Soluble Log S (Ali) -2.87 Solubility 2.24e-01 mg/ml ; 1.36e-03 mol/l Class Soluble Log S (SILICOS-IT) -1.28 Solubility 8.67e+00 mg/ml ; 5.28e-02 mol/l Class Soluble
Vanillic acid	GI absorption High BBB permeant No P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -6.31 cm/s	PAINS 0 alert Brenk 0 alert Leadlikeness No; 1 violation: MW<250 Synthetic accessibility 1.42	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes Muegge No; 1 violation: MW<200 Bioavailability Score 0.85	Formula C8H8O4 Molecular weight 168.15 g/mol Num. heavy atoms 12 Num. arom. heavy atoms 6 Fraction Csp3 0.12 Num. rotatable bonds 2 Num. H-bond acceptors 4 Num. H-bond donors 2 Molar Refractivity 41.92	Log Po/w (iLOGP) 1.40 Log Po/w (XLOGP3) 1.43 Log Po/w (WLOGP) 1.10 Log Po/w (MLOGP) 0.74 Log Po/w (SILICOS-IT) 0.73 Consensus Log Po/w 1.08	Log S (ESOL) -2.02 Solubility 1.60e+00 mg/ml ; 9.52e-03 mol/l Class Soluble Log S (Ali) -2.44 Solubility 6.15e-01 mg/ml ; 3.66e-03 mol/l Class Soluble Log S (SILICOS-IT) -1.32 Solubility 8.10e+00 mg/ml ; 4.82e-02 mol/l Class Soluble

				TPSA 66.76 Å²		
Syringic acid	GI absorption High BBB permeant No P-gp substrate No CYP1A2 inhibitor No CYP2C19 inhibitor No CYP2C9 inhibitor No CYP2D6 inhibitor No CYP3A4 inhibitor No Log Kp (skin permeation) -6.77 cm/s	PAINS 0 alert Brenk 0 alert Leadlikeness No; 1 violation: MW<250 Synthetic accessibility 1.70	Lipinski Yes; 0 violation Ghose Yes Veber Yes Egan Yes Muegge No; 1 violation: MW<200 Bioavailability Score 0.56	Formula C9H10O5 Molecular weight 198.17 g/mol Num. heavy atoms 14 Num. arom. heavy atoms 6 Fraction Csp3 0.22 Num. rotatable bonds 3 Num. H-bond acceptors 5 Num. H-bond donors 2 Molar Refractivity 48.41 TPSA 75.99 Å²	Log Po/w (iLOGP) 1.54 Log Po/w (XLOGP3) 1.04 Log Po/w (WLOGP) 1.11 Log Po/w (MLOGP) 0.49 Log Po/w (SILICOS-IT) 0.77 Consensus Log Po/w 0.99	Log S (ESOL) -1.84 Solubility 2.84e+00 mg/ml ; 1.44e-02 mol/l Class Very soluble Log S (Ali) -2.23 Solubility 1.18e+00 mg/ml ; 5.94e-03 mol/l Class Soluble Log S (SILICOS-IT) -1.46 Solubility 6.93e+00 mg/ml ; 3.50e-02 mol/l Class Soluble