

Research Article

Title;

Effects of Quercetin and Derivatives on NAMPT/Sirtuin-1 Metabolic Pathway in Neuronal Cells: An Approach to Mitigate Chemotherapy-Induced Cognitive Impairment

Author Information

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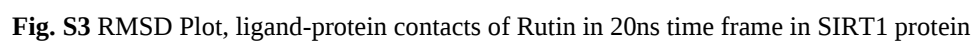
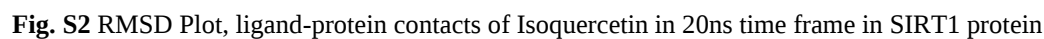
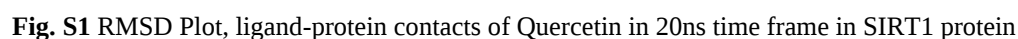
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SIRT1: Molecular Dynamics



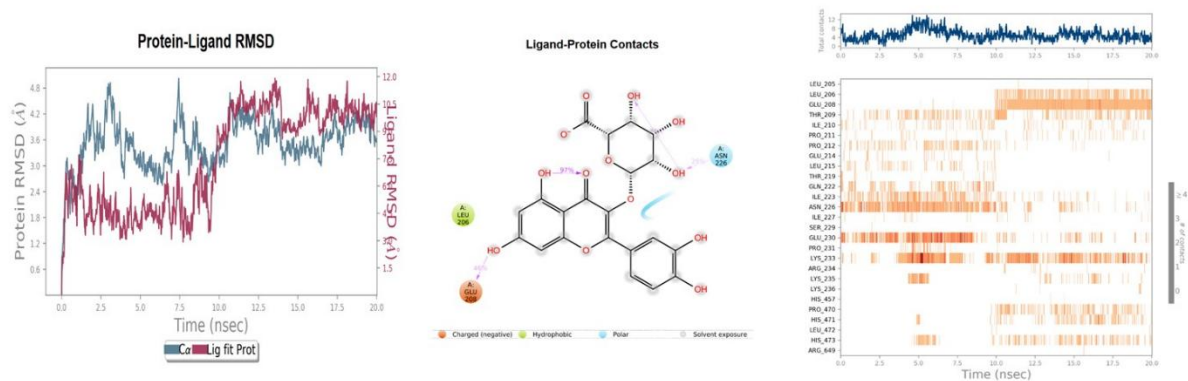


Fig. S4 RMSD Plot, ligand-protein contacts of Miquelianin in 20ns time frame in SIRT1 protein

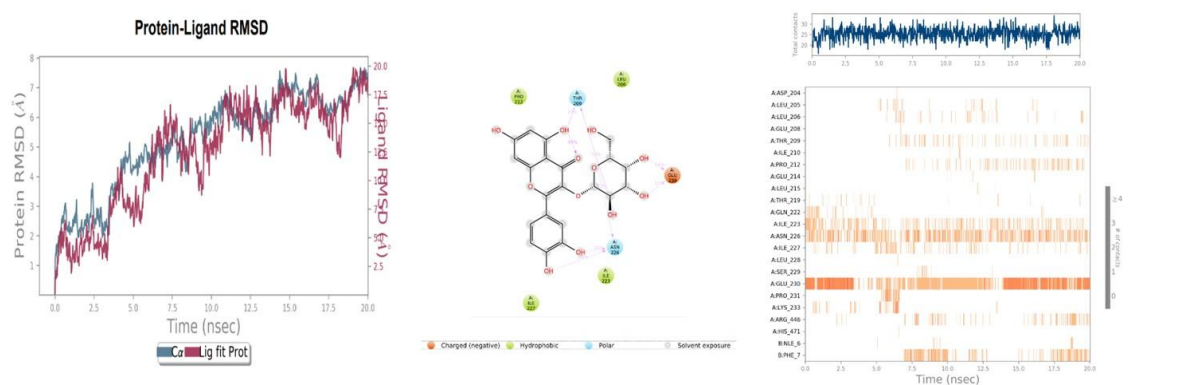


Fig. S5 RMSD Plot, ligand-protein contacts of Hyperoside in 20ns time frame in SIRT1 protein

NAMPT: Molecular Dynamics

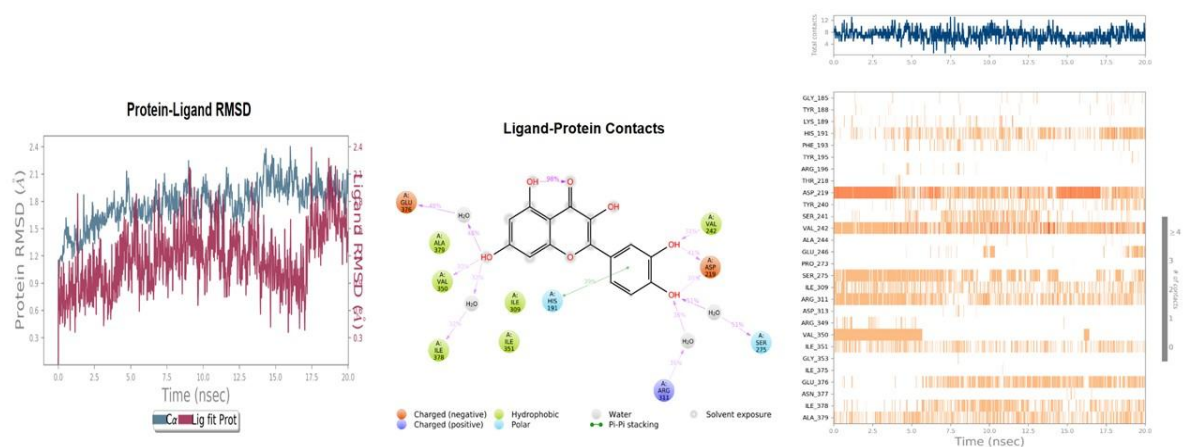


Fig. S6 RMSD Plot, ligand-protein contacts of Quercetin in 20ns time frame in NAMPT protein

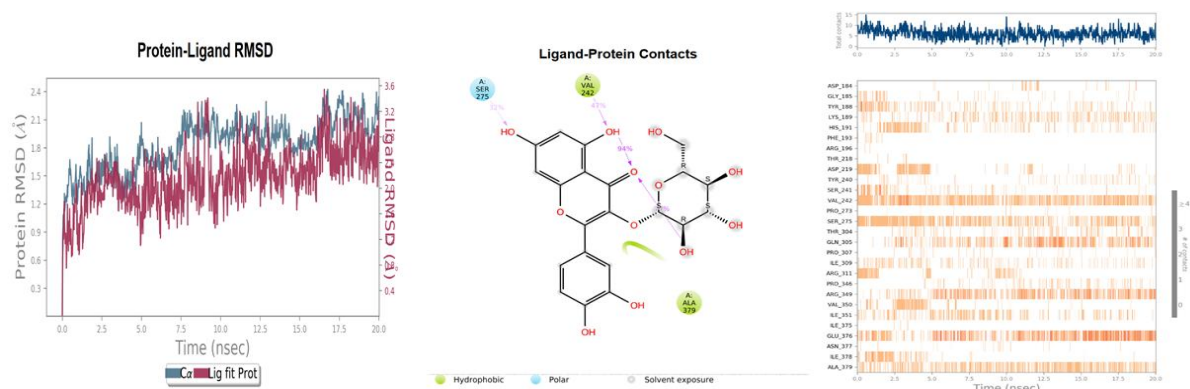


Fig. S7 RMSD Plot, ligand-protein contacts of Isoquercetin in 20ns time frame in NAMPT protein

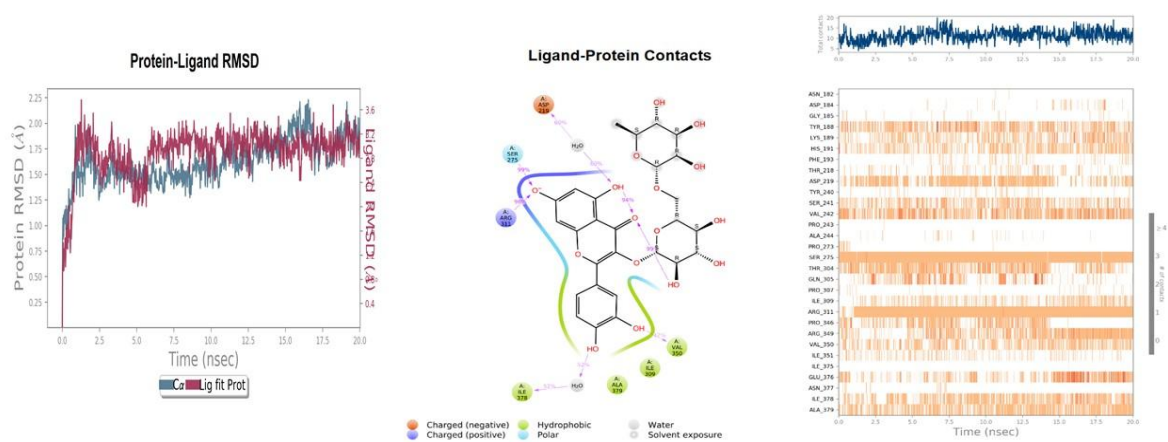


Fig.S8 RMSD Plot, ligand-protein contacts of Rutin in 20ns time frame in NAMPT protein

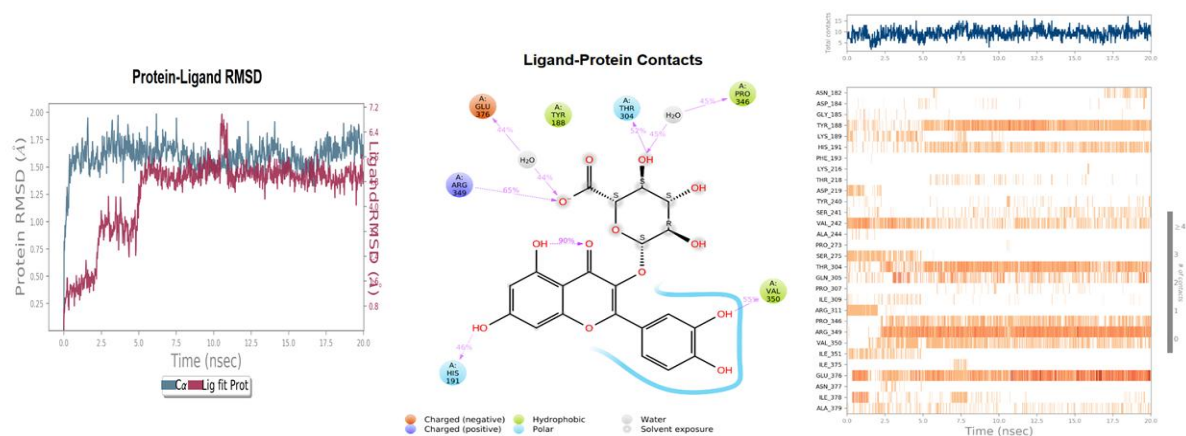


Fig. S9 RMSD Plot, ligand-protein contacts of Miquelianin in 20ns time frame in NAMPT protein

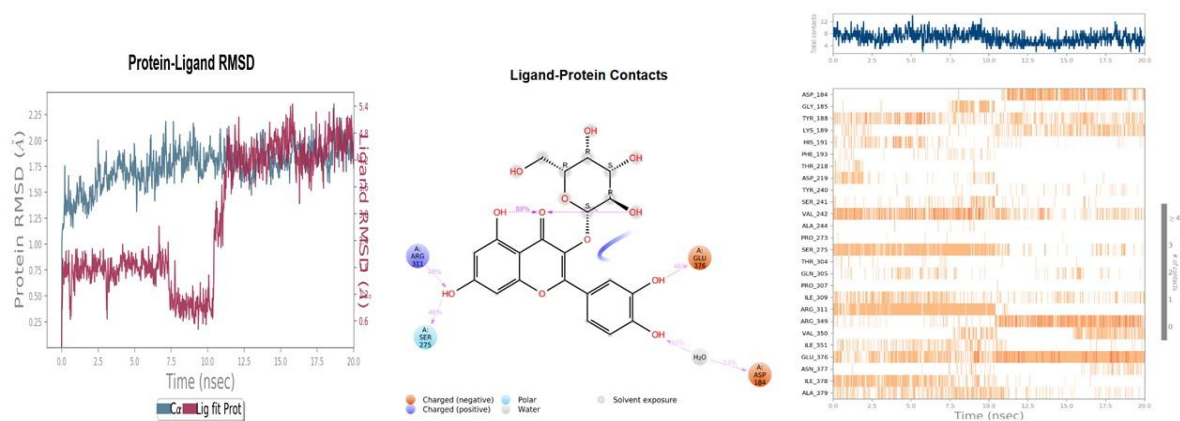
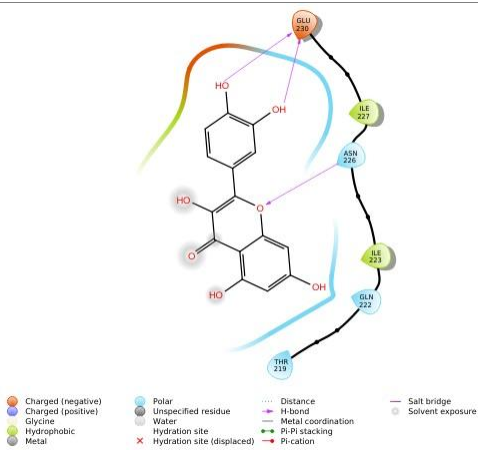
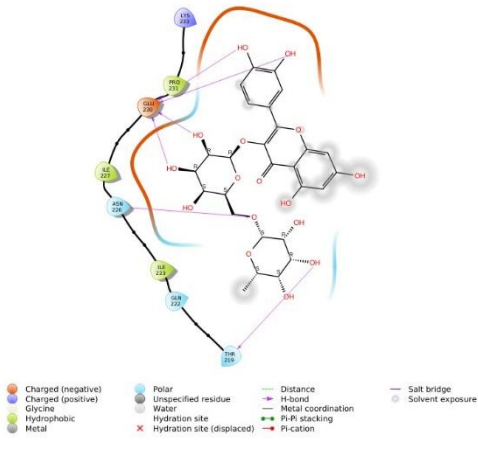
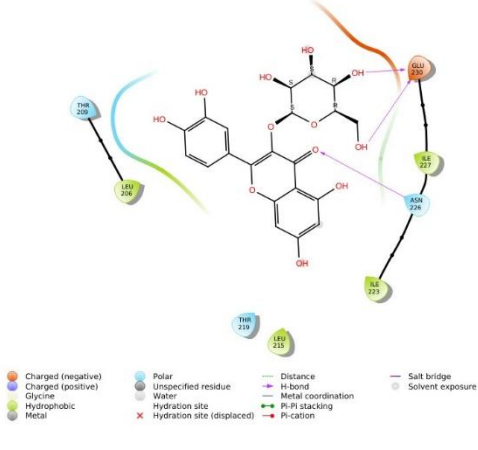


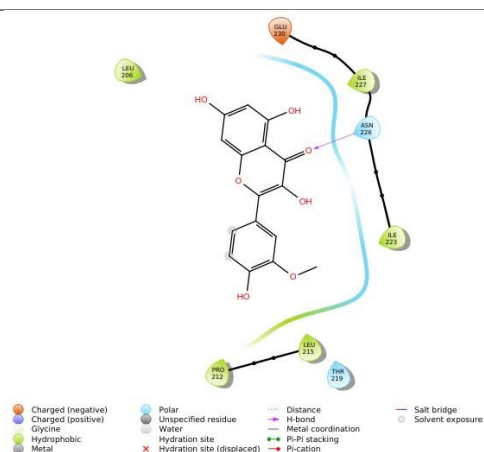
Fig. S10 RMSD Plot, ligand-protein contacts of Hyperoside in 20ns time frame in NAMPT protein

Tables

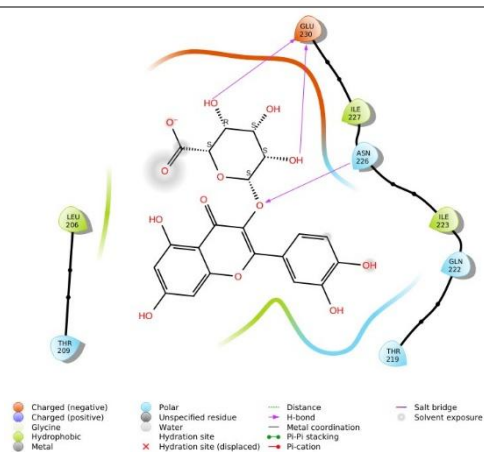
Ligand	Hydrogen bonding	Hydrophobic Interactions	Hydrophilic Interactions	2-D Interaction diagram
Co-ligand (4TQ)	GLU 230 (negative charge)	LEU 215, PRO 212, PRO 211, LEU 206, ILE 223, ILE 227, PRO 230	THR 209, ASN 226, SER 229	

Quercetin	2GLU 230, ASN 226	ILE 223, ILE 227	THR 219, ASN 226, GLN 222	
Rutin	4 GLU 230, ASN 226	PRO 231, ILE 223, ILE 227	THR 219, ASN 226, GLN 222 Other: LYS 233(positive charge)	
Hyperoside	2GLU 230, ASN 226	LEU 215, ILE 223, ILE 227, LEU 206	THR 209, THR 219, ASN 226	

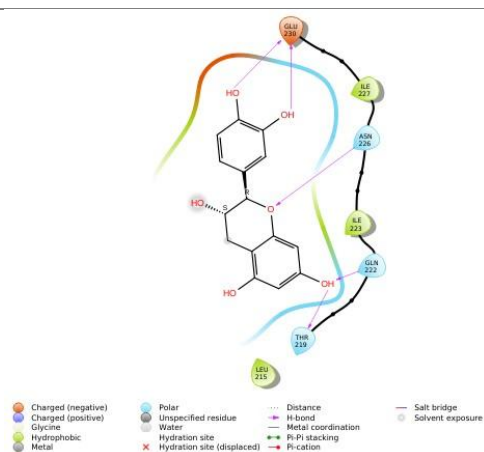
Isorhamnetin	ASN 226	LEU 215, ILE 223, ILE 227, LEU 206, PRO 212	THR 219, ASN 226
		Other: GLU 230(negative charge)	



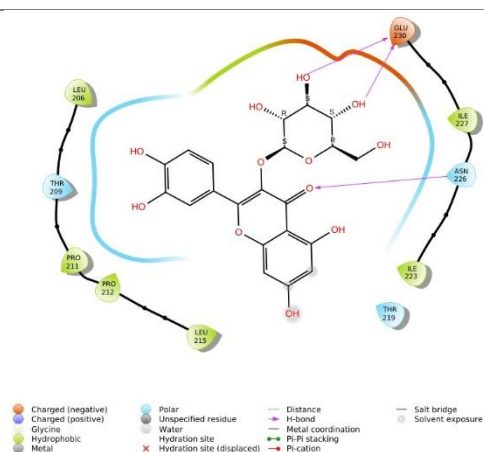
Miquelianin	2GLU 230, ASN 226	ILE 223, ILE 227, LEU 206	THR 209, THR 219, ASN 226, GLN 222
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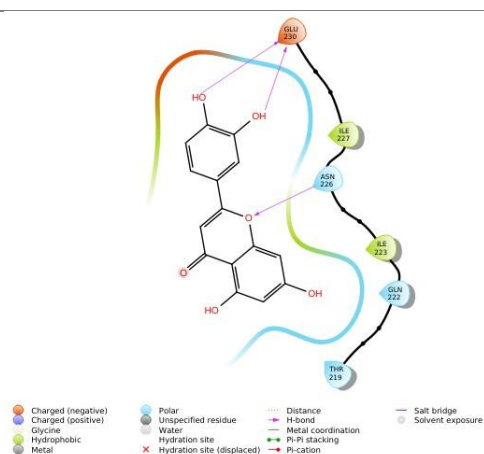
Catechin	2GLU 230, ASN 226, GLN 222, THR 219	ILE 223, ILE 227, LEU 215	THR 219, ASN 226, GLN 222
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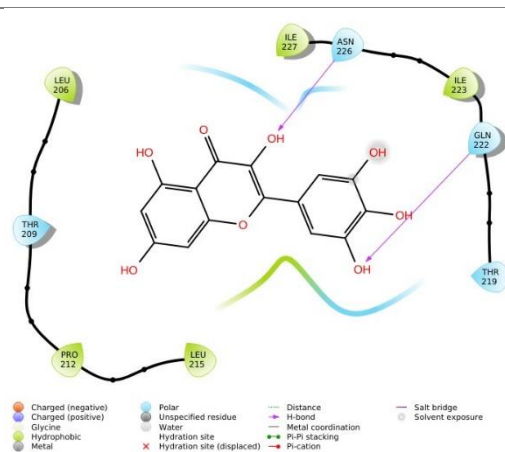
Isoquercetin 2GLU 230, ASN 226 ILE 223, ILE 227, LEU 206, PRO 211, PRO 212, LEU 215 THR 209, THR 219, ASN 226



Luteolin 2GLU 230, ASN 226 ILE 223, ILE 227 THR 209, THR 219, ASN 226

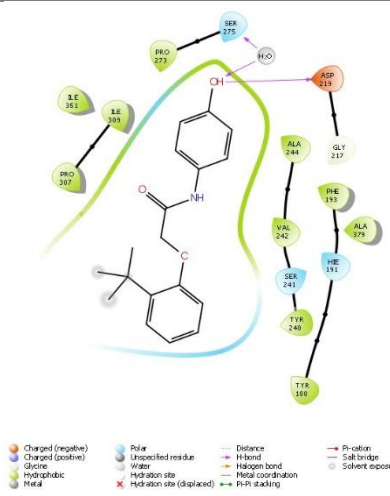
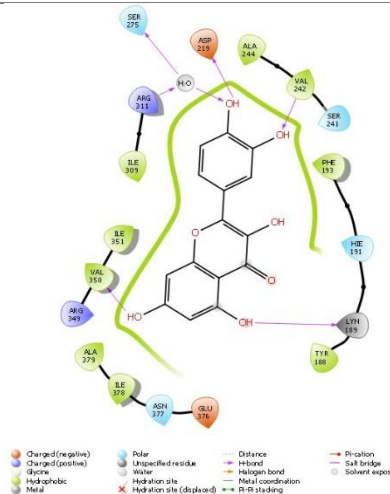
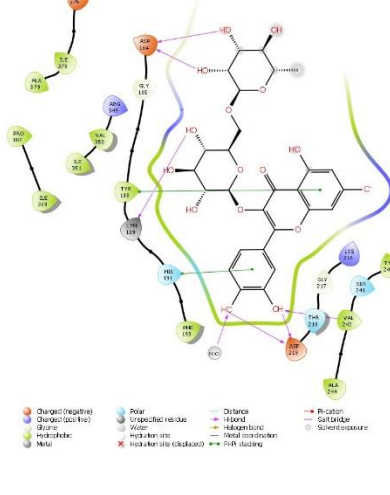


Myricetin GLN 222, ASN 226 ILE 223, ILE 227, LEU 206, PRO 212, LEU 215 THR 209, THR 219, ASN 226, GLN 222



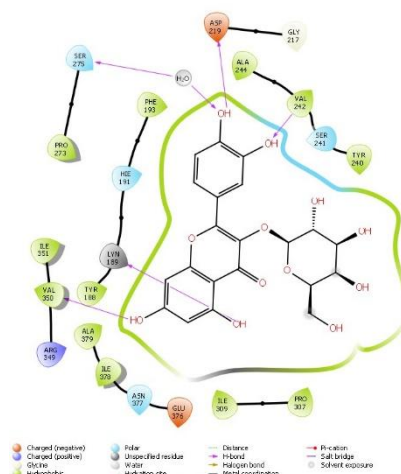
Morin	GLU 230, ASN 226	ILE 223, ILE 227, LEU 215	GLN 222, THR 219, ASN 226	Charged (negative) Charged (positive) Glycine Hydrophobic Metal Polar Unspecified residue Water Hydration site Hydration site (displaced) Distance H-bond Metal coordination Pi-Pi stacking Pi-cation Salt bridge Solvent exposure
Apigenin	GLU 230, ASN 226	ILE 223, ILE 227	GLN 222, THR 219, ASN 226	Charged (negative) Charged (positive) Glycine Hydrophobic Metal Polar Unspecified residue Water Hydration site Hydration site (displaced) Distance H-bond Metal coordination Pi-Pi stacking Pi-cation Salt bridge Solvent exposure
Taxifolin	2GLU 230, ASN 226	ILE 223, ILE 227	THR 219, GLN 222, ASN 226	Charged (negative) Charged (positive) Glycine Hydrophobic Metal Polar Unspecified residue Water Hydration site Hydration site (displaced) Distance H-bond Metal coordination Pi-Pi stacking Pi-cation Salt bridge Solvent exposure

Table S1: 2D interaction diagrams including interactions with SIRT1 protein

Ligand	Hydrogen bonding	Hydrophilic Interactions	Hydrophobic Interactions	2-D Interaction diagram
Co-ligand (NAT)	ASP 219, SER 275	SER 275, SER 241, HIE 191	PRO 273, ILE 351, ILE 309, PRO 307, ALA 244, VAL 242, PHE 193, ALA 379, TYR 188, TYR 240	
Quercetin	ASP 219, SER 275, VAL 242, VAL 350, LYN 189	SER 275, SER 241, HIE 191, ASN 377	ILE 351, ILE 309, ALA 244, VAL 242, PHE 193, ALA 379, TYR 188, VAL 350, ILE 378	
Rutin	LYN 189, ASP 219, VAL 242, ASP 184	SER 241, THR 218, HIE 191	ILE 378, ALA 379, PRO 307, ILE 309, ILE 351, VAL 350, TYR 188, PHE 193, VAL 242, ALA 244, TYR 240	

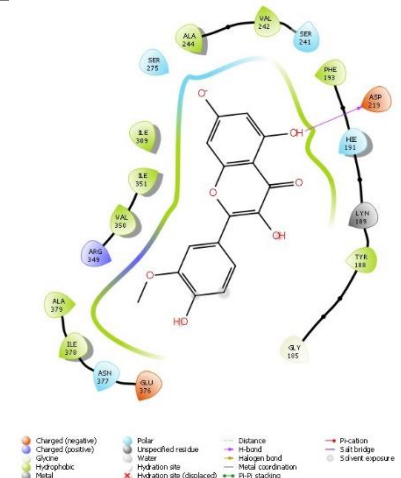
Hyperoside

ASP 219,	SER 275, SER	ILE 351, ALA
LYN 189,	241, HIE 191,	379, PRO 273,
SER 275,	ASN 377	PRO 307, ILE
VAL 242,		309, VAL 242,
VAL 350		ALA 244, TYR
		188, ILE 378,
		PHE 193, TYR
		240, VAL 350



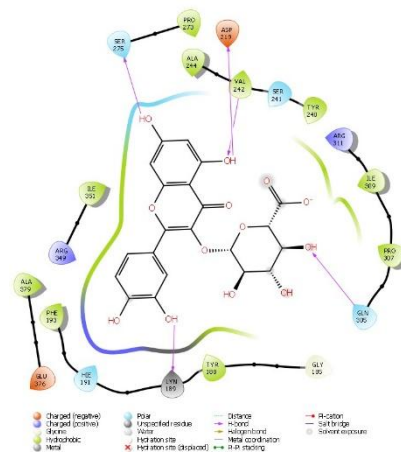
Isorhamnetin

ASP 219	SER 275, SER	ILE 351, ALA
	241, HIE 191,	379, ILE 309,
	ASN 377	VAL 242, ALA
		244, TYR 188,
		PHE 193, VAL
		350, ILE 378

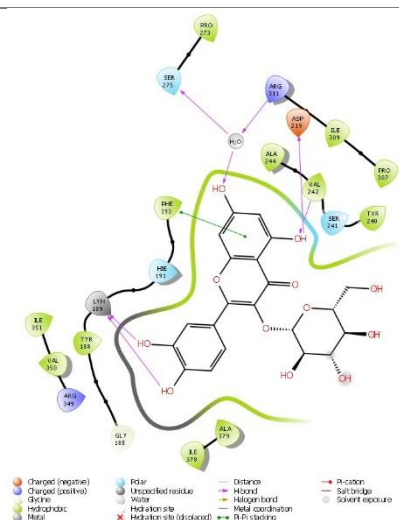


Miquelianin

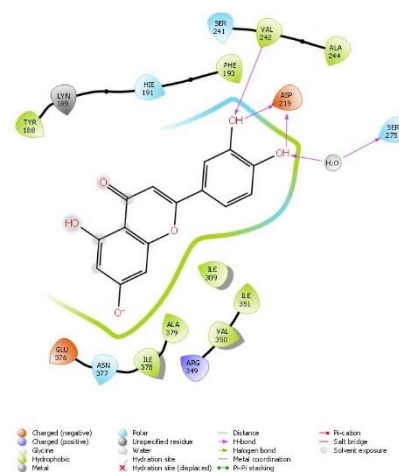
ASP 219,	SER 275, SER	PRO 273, ILE
LYN 189,	241, HIE 191,	309, PRO 307,
VAL 242,	GLN 305	TYR 240, VAL
SER 275,		242, ALA 244,
GLN 305		PHE 193, ILE
		351, VAL 350,
		TYR 188, ALA
		379, ILE 378



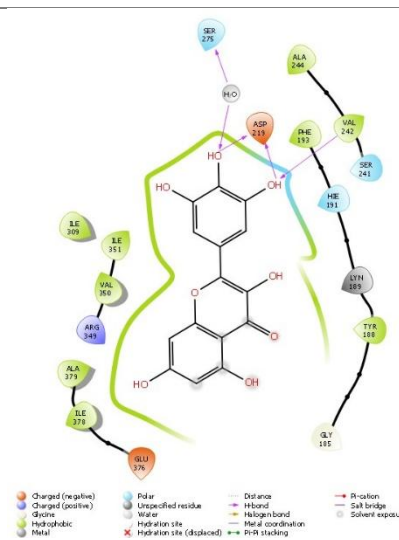
Isoquercetin ASP 219, SER 275, SER PRO 273, ILE
LYN 189, 241, HIE 191 309, PRO 307,
SER 275. TYR 240, VAL
ARG 311, 242, ALA 244,
VAL 242 PHE 193, ILE
351, VAL 350,
TYR 188, ALA
379, ILE 378



Luteolin ASP 219, SER 241, HIE ALA 244, VAL
SER 275, 191, SER 275, 242, PHE 193,
VAL 242, ASN 377 TYR 188, ILE
351, VAL 350,
ILE 309, ILE
378, ALA 379,
ILE 351



Myricetin ASP 219, SER 241, HIE ALA 244, VAL
SER 275, 191, SER 275 242, PHE 193,
VAL 242, TYR 188, VAL
350, ILE 309,
ILE 378, ALA
379, ILE 351



Morin	ASP 219, SER 275	SER 241, HIE 191, SER 275	ALA 244, VAL 242, TYR 188, ILE 309, ALA 379, ILE 351, Pi-Pi : PHE 193	Legend: Charged (negative) (red circle), Charged (positive) (blue circle), Glycine (green circle), Hydrophobic (yellow circle), Metal (grey circle), Polar (light blue circle), Unspecified residue (light green circle), Water (blue circle), Hydrogen bond (dashed line), Hydrophobic site (dashed line), Hydration site (displaced) (red X), Distance (dashed line), H-bond (dashed line), Halogen bond (dashed line), Metal coordination (dashed line), Pi-Pi stacking (dashed line), Pi-cation (dashed line), Salt bridge (dashed line), Solvent exposure (dashed line)
Apigenin	ASP 219, SER 275	SER 241, HIE 191, SER 275	ALA 244, VAL 242, PHE 193, TYR 188, VAL 350, ILE 309, ALA 379, ILE 351	Legend: Charged (negative) (red circle), Charged (positive) (blue circle), Glycine (green circle), Hydrophobic (yellow circle), Metal (grey circle), Polar (light blue circle), Unspecified residue (light green circle), Water (blue circle), Hydrogen bond (dashed line), Hydrophobic site (dashed line), Hydration site (displaced) (red X), Distance (dashed line), H-bond (dashed line), Halogen bond (dashed line), Metal coordination (dashed line), Pi-Pi stacking (dashed line), Pi-cation (dashed line), Salt bridge (dashed line), Solvent exposure (dashed line)
Taxifolin	ASP 219, SER 275, VAL 242, HIE 191	SER 241, HIE 191, SER 275	ALA 244, VAL 242, PHE 193, TYR 188, VAL 350, ILE 309, ALA 379, ILE 351, ILE 378	Legend: Charged (negative) (red circle), Charged (positive) (blue circle), Glycine (green circle), Hydrophobic (yellow circle), Metal (grey circle), Polar (light blue circle), Unspecified residue (light green circle), Water (blue circle), Hydrogen bond (dashed line), Hydrophobic site (dashed line), Hydration site (displaced) (red X), Distance (dashed line), H-bond (dashed line), Halogen bond (dashed line), Metal coordination (dashed line), Pi-Pi stacking (dashed line), Pi-cation (dashed line), Salt bridge (dashed line), Solvent exposure (dashed line)

Table S2: 2D interaction diagrams including interactions with NAMPT protein

Treatment	Concentration (μ M)	Percentage of Cell viability in SH-SY5Y Cells	
		Undifferentiated	Differentiated
Normal Control	-	100	100
Methotrexate+5-Fluorouracil	4.179	49.53 $\pm$ 2.363####	55.46 $\pm$ 2.664####
Quercetin	0.00096	60.83 $\pm$ 1.092****	67.26 $\pm$ 0.8592****
	0.0048	63.14 $\pm$ 1.429****	72.02 $\pm$ 1.375****
	0.24	63.79 $\pm$ 1.388****	73.66 $\pm$ 0.601****
	0.12	64.39 $\pm$ 1.301****	74.70 $\pm$ 0.343****
	0.6	62.76 $\pm$ 0.889****	77.53 $\pm$ 1.289****
	3	60.96 $\pm$ 1.303****	70.98 $\pm$ 1.632****
	15	59.76 $\pm$ 0.480****	69.20 $\pm$ 0.773****

Table S3: Effect of 2 h pretreatment of quercetin on cell viability on MF-induced toxicity in SH-SY5Y cells. **A)** Undifferentiated SH-SY5Y cells **B)** Differentiated SH-SY5Y cells. Data represents mean $\pm$ SEM analysed by One-way ANOVA followed by Dunnet's post-hoc test. ####p<0.0001 compared to normal control, ****p<0.0001 compared to MF control.

Treatment	Concentration (μ M)	Percentage of Cell viability in SH-SY5Y Cells	
		Undifferentiated	Differentiated
Normal Control	-	100	100
Methotrexate+5-Fluorouracil	4.179	49.53 $\pm$ 2.363####	55.46 $\pm$ 2.664####
Rutin	0.128	60.24 $\pm$ 1.182****	73.21 $\pm$ 1.203****
	0.64	59.76 $\pm$ 0.594****	74.23 $\pm$ 0.839****
	3.2	64.13 $\pm$ 2.016****	74.70 $\pm$ 0.343****
	16	64.13 $\pm$ 0.926****	73.07 $\pm$ 1.976****
	80	58.14 $\pm$ 1.157****	76.64 $\pm$ 0.601****
	400	61.30 $\pm$ 1.049****	66.67 $\pm$ 1.718****
	2000	56.77 $\pm$ 0.816****	55.51 $\pm$ 1.289

Table S4: Effect of 2 h pretreatment of rutin on cell viability on MF-induced toxicity in SH-SY5Y cells. **A)** Undifferentiated SH-SY5Y cells **B)** Differentiated SH-SY5Y cells. Data represents mean±SEM analysed by One-way ANOVA followed by Dunnet's post-hoc test. #####p<0.0001 compared to normal control. ****p<0.0001 compared to MF control.

Treatment	Concentration (µM)	Percentage of Cell viability in SH-SY5Y Cells	
		Undifferentiated	Differentiated
Normal Control	-	100	100
Methotrexate+5-Fluorouracil	4.192	49.53±2.363#####	55.46±2.664####
Isoquercetin	0.128	60.88±0.546****	80.51±1.976****
	0.64	58.10±2.875***	72.77±1.976****
	3.2	63.10±2.605****	82.29±0.773****
	16	62.12±2.919****	86.61±1.031****
	80	57.50±3.401***	86.76±0.601****
	400	52.19±0.926	70.54±0.171****
	2000	43.34±1.112	55.51±0.257

Table S5: Effect of 2 h pretreatment of isoquercetin on cell viability on MF-induced toxicity in SH-SY5Y cells. **A)** Undifferentiated SH-SY5Y cells **B)** Differentiated SH-SY5Y cells. Data represents mean±SEM analysed by One-way ANOVA followed by Dunnet's post-hoc test. #####p<0.0001 compared to normal control. ***p<0.001, ****p<0.0001 compared to MF control.

Treatment	Concentration (µM)	Neurite Length
Normal Control	-	85.38±6.717
Methotrexate+5-Fluorouracil	4.179	41.77±4.715####
Quercetin	0.024	81.57±3.805****
	0.12	81.63±3.428****
	0.6	82.53±4.624****
	3	80.44±4.203****
	15	76.74±5.916***
Rutin	3.2	79.01±4.500****

	16	79.72±4.537****
	80	83.83±5.148****
	400	64.85±3.451*
Isoquercetin	3.2	75.15±3.798****
	16	81.07±3.769****
	80	85.35±4.738****
	400	73.11±4.606****

Table S6: Effect of 2h pretreatment of QRT, RUT and IQRT concentrations on the neurite length on MF-induced toxicity in differentiated SH-SY5Y cells after 48h of incubation. Data represents mean±SEM of three trials analysed by One-way ANOVA followed by Dunnet's post-hoc test. #####p<0.0001 compared to normal control group, *p<0.05, ***p<0.001, ****p<0.0001 compared to MF control group