Electronic Supplementary Material (ESI) for RSC Advances.

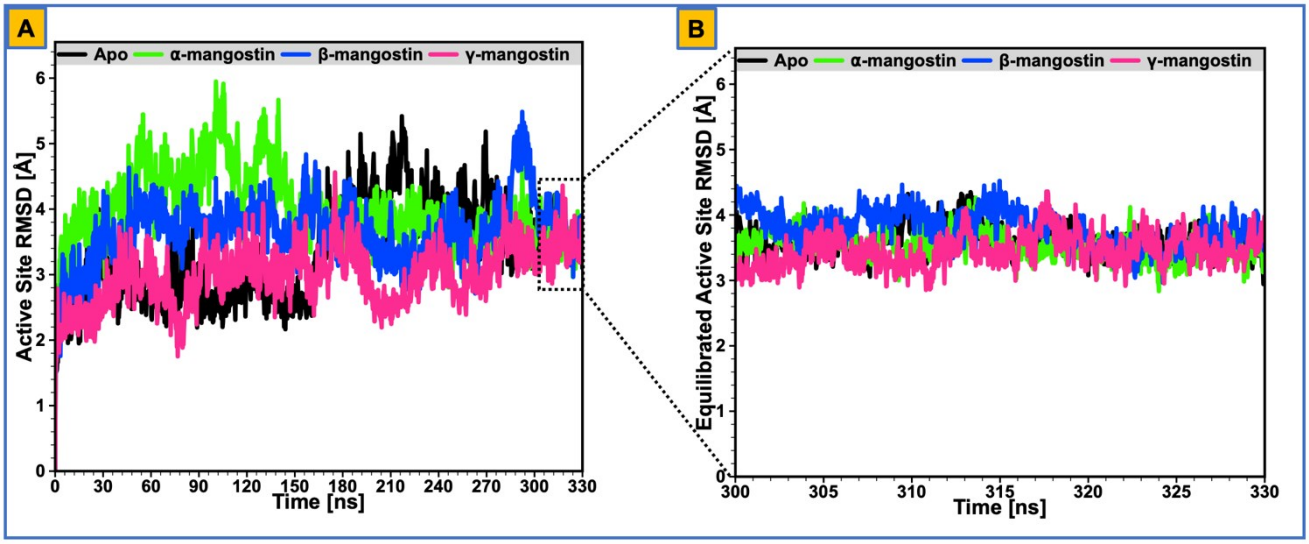
Structural Alterations in The Catalytic Core of hSIRT2 Enzyme Predict Therapeutic Benefits of *Garcinia mangostana* Derivatives in Alzheimer's Disease: Molecular Dynamic Study

Oluwole B. Akawa[1,2], Temitayo Subair[1], Opeyemi Soremekun[1], Fisayo A. Olotu[1], Mahmoud E.S. Soliman[1]*

[1]Molecular Bio-computation and Drug Design Laboratory, School of Health Sciences, University of KwaZulu-Natal, Westville Campus, Durban 4001, South Africa

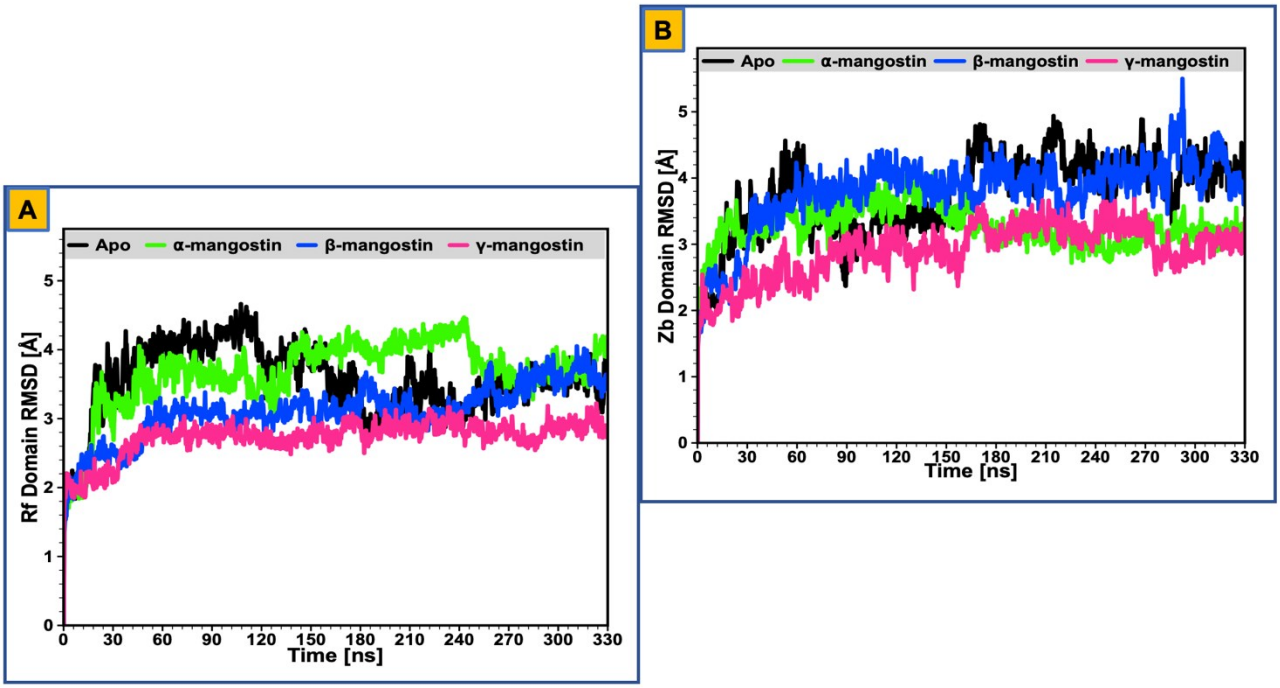
[2]Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, Afe Babalola University, Ado Ekiti, Nigeria

SUPPLEMENTARY TABLES & FIGURES

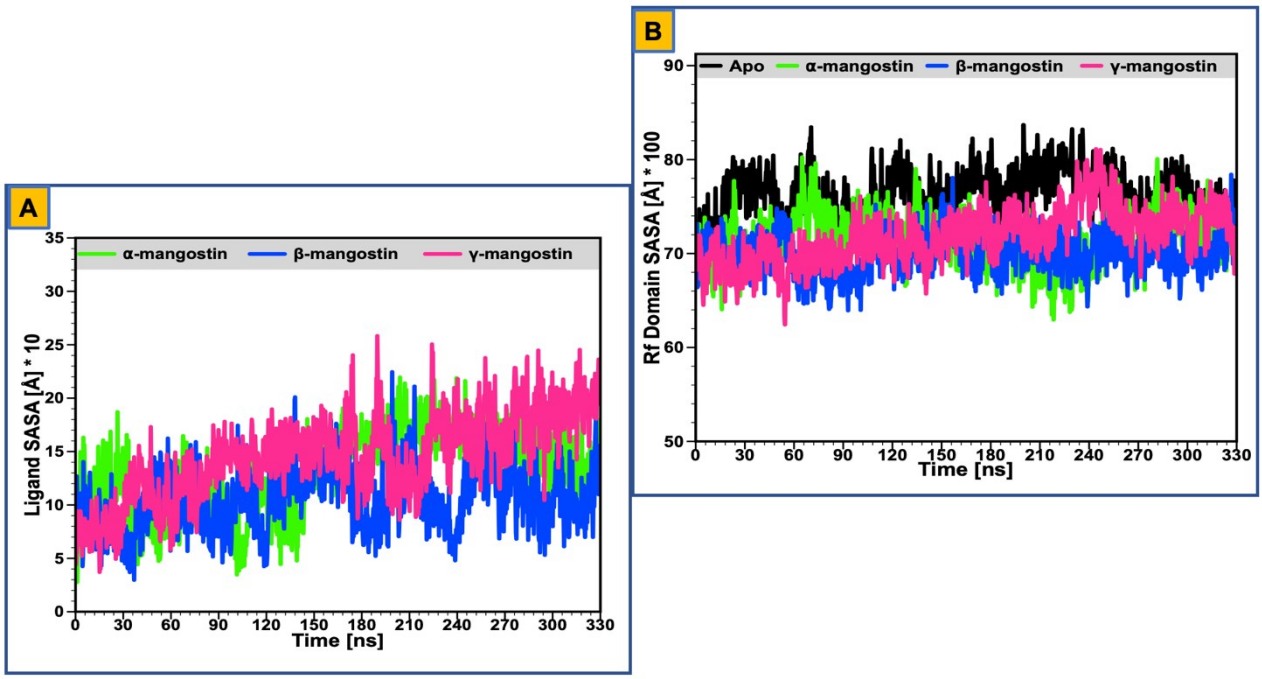


SUPPLEMENTARY FIGURES

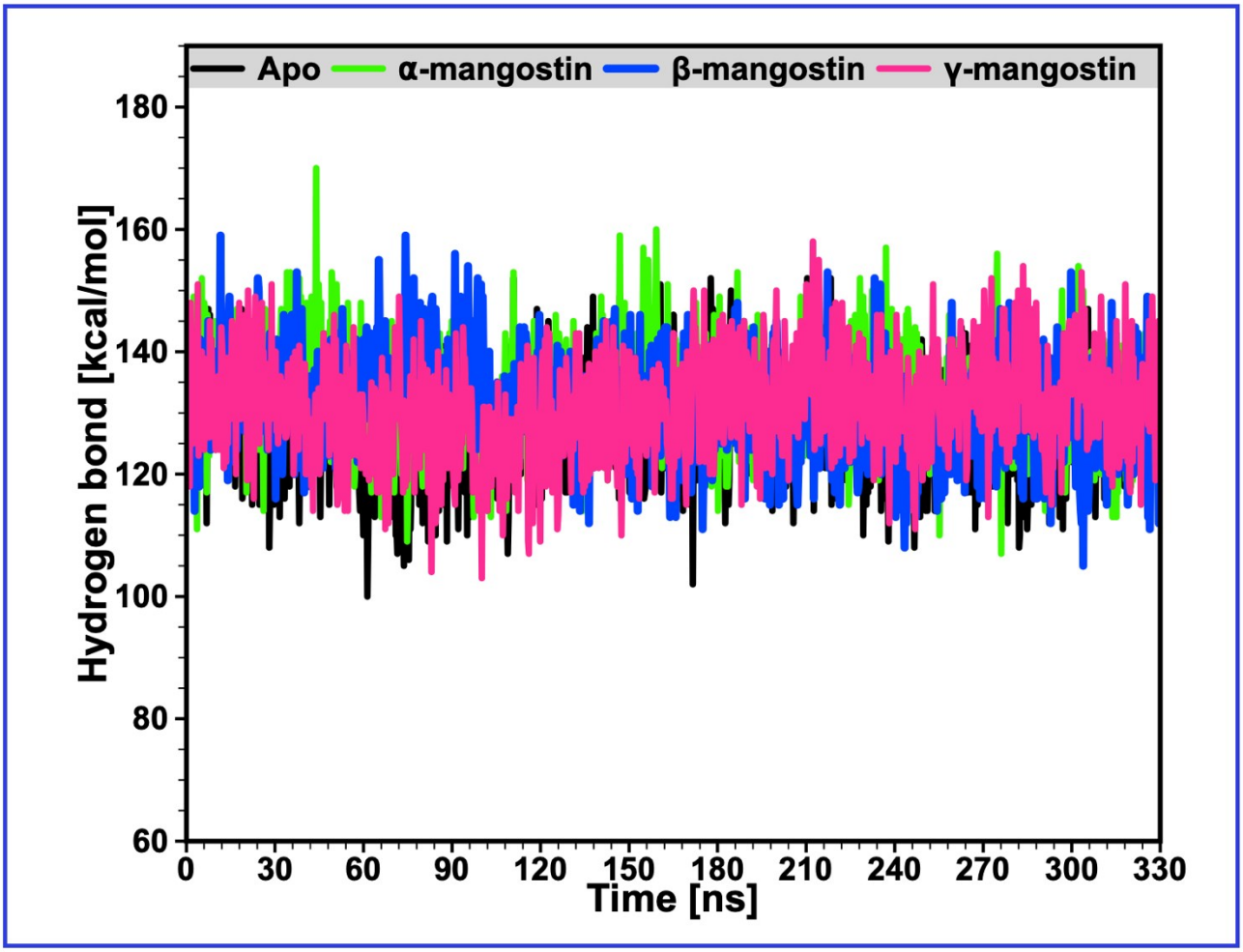
Suppl. Figure 1: [A] RMSD plots showing the binding pocket stability of unbound hSIRT2 enzyme (black), α-mangostin-bound (light green), β-mangostin-bound (blue) and γ-mangostin-bound (strawberry) across 330 ns simulation run. **[B]** Post-equilibrated active site RMSD plots (showing the region of convergence starting from 300 ns) of unbound hSIRT2 enzyme (black), α-mangostin-bound (light green), β-mangostin-bound (blue) and γ-mangostin-bound (strawberry).



Suppl. Figure 2: Structural analysis of the catalytic core of unbound (black), α-mangostin-bound (light green), β-mangostin-bound (blue) and γ-mangostin-bound hSIRT2 enzyme (strawberry). Comparative Cα RMSD showing stability and atomistic deviations in Rossman-fold domain **[A]** and Zn^{2+}-binding domain **[B].**



Suppl. Figure 3: [A] Structural SASA analysis plot of the catalytic core of hSIRT2 enzyme when ligand bound to α-mangostin (light green), β-mangostin (blue) and γ-mangostin (strawberry)**. [B]** Structural analysis of the catalytic core of unbound (black), α-mangostin-bound (light green), β-mangostin-bound (blue) and γ-mangostin-bound hSIRT2 enzyme (strawberry) showing comparative SASA plot in the Rossman-fold domain**.**



Suppl. Figure 4: Hydrogen bond analysis plots depicting intramolecular and intermolecular hydrogen bond energy contributions in the apo hSIRT2 enzyme (black), α-mangostin (light green), β-mangostin (deep blue) and γ-mangostin (strawberry).

SUPPLEMENTARY TABLES

Suppl. Table 1: Average RMSD, RMSF, RoG and SASA values estimated (including whole system and catalytic core) of all systems (both bound and unbound).

	hSIRT2 Apo	**α-mangostin-bound**	**β-mangostin-bound**	**γ-mangostin-bound**
RMSDo (Å)	3.49 ± 0.15	3.21 ± 0.25	3.24 ± 0.54	3.03 ± 0.67
RMSDx (Å)	3.93 ± 0.67	3.84 ± 0.46	3.66 ± 0.38	3.34 ± 0.72
RMSDy(Å)	-	1.60 ± 0.11	1.42 ± 0.22	1.57 ± 0.34
RMSFx (Å)	1.97 ± 0.62	2.11 ± 0.34	1.93 ± 0.55	1.66 ± 0.27
RoGx (Å)	21.59 ± 0.36	21.02 ± 0.22	20.49 ± 0.37	21.08 ± 0.30
SASAx (Å)	1454.30 ± 100.13	646.09 ± 72.70	830.13 ± 128.02	603.11 ± 158.31
SASAy (Å)	-	164.12 ± 36.30	133.92 ± 29.00	104.16 ± 37.54

RMSD = Root mean square deviation; **RMSF** = Root mean square fluctuation, **RoG** = Radius of gyration; **SASA** = Solvent accessible surface area. **RMSDo** = Whole protein RMSD; **RMSDx** = Catalytic core RMSD; **RMSDy** = Ligand RMSD; **RMSFx** = Catalytic core RMSF; **RoGx** = Catalytic core RoG; **SASAx** = Catalytic core SASA; **SASAy** = Ligand SASA

Suppl. Table 2: Average RMSD, RMSF, B Factor and SASA values estimated for all Rossman-fold domain and Zn^{2+}-binding domain of all the systems (both bound and unbound).

	hSIRT2 Apo	**α-mangostin-bound**	**β-mangostin-bound**	**γ-mangostin-bound**
B-FACTORi (Å)	107.77 ± 88.00	87.08 ± 55.18	83.22 ± 54.21	82.56 ± 53.57
B-FACTORr (Å)	101.26 ± 140.63	75.04 ± 129.45	72.47 ± 124.22	65.34 ± 118.19
B-FACTORx (Å)	117.54 ± 76.48	118.00 ± 55.99	106.46 ± 100.51	92.04 ± 51.11
RMSDi (Å)	3.76 ± 0.46	3.35 ± 0.22	3.69 ± 0.23	3.22 ± 0.6
RMSDr (Å)	3.62 ± 0.43	3.59 ± 0.39	3.31 ± 0.35	2.89 ± 0.05
RMSFi (Å)	1.85 ± 0.80	1.69 ± 0.67	1.65 ± 0.25	1.63 ± 0.78
RMSFr (Å)	1.56 ± 1.22	1.45 ± 0.96	1.39 ± 0.86	1.32 ± 0.94
SASAi (Å)	7723.46 ± 99.57	7254.65 ± 92.85	7133.51 ± 58.19	7099.12 ± 85.13
SASAr (Å)	7651.12 ± 109.72	7144.57 ± 91.82	7014.74 ± 84.23	7088.17 ± 85.43

B-FACTOR = Debye-Waller factor; **RMSD** = Root mean square deviation; **RMSF** = Root mean square fluctuation; **SASA** = Solvent accessible surface area; **i** = Zinc-binding domain; **r =** Rossman-fold domain; **x** = active site

Suppl. Table 3: Hydrogen bond interactions between *G. mangostana* phytochemicals (α-mangostin, β-mangostin and γ-mangostin**)** and the residual amino acids of hSIRT2 enzyme during 330 ns simulation run.

Complexes	Direct Hydrogen Bonds						
	Donor			**Acceptor**		**Distance (Å)**	**Occup-ancy (%)**
α-mangostin-bound	Ala85	H	N	**α-mangostin**	O4	2.92	10.95
	α-mangostin	HO1	O5	Gln265	OE1	2.69	5.69
	α-mangostin	HO1	O5	Ser263	OG	2.77	4.37
	Ser263	H	N	**α-mangostin**	O5	2.93	1.19
	α-mangostin	HO	O5	Gln167	O	2.64	1.12
β-mangostin-bound	**β-mangostin**	H	O3	Glu116	OE1	2.67	14.35
	Ala85	H	N	**β-mangostin**	O4	2.94	11.32
	Gln167	HE21	NE2	**β-mangostin**	O1	2.87	10.73
	His187	HE2	NE2	**β-mangostin**	O2	2.87	2.54
	Ser263	HG	OG	**β-mangostin**	O5	2.83	1.17
γ-mangostin-bound	**γ-mangostin**	H3	O5	Pro115	O	2.73	23.80
	Ala85	H	N	**γ-mangostin**	O4	2.91	15.26
	γ-mangostin	H3	O3	Glu116	OE1	2.67	10.27
	His187	HE2	NE2	**γ -mangostin**	O3	2.87	5.54
	γ-mangostin	H	ON	Phe119	OE2	2.67	4.37
	γ-mangostin	H2	O5	Asn168	OD1	2.67	4.34
	Ser263	HG	OG	**γ-mangostin**	O5	2.83	1.17