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Anti-Aging Potential of *Moringa oleifera* Bioactive Compounds: A Molecular Docking Approach Targeting Sirtuin Proteins

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Abstract

Moringa oleifera has long been valued in traditional skincare, but its molecular interactions with key aging regulators remain poorly understood. This study elucidates the anti-aging potential of *Moringa oleifera* bioactive compounds through their modulation of sirtuin proteins (SIRT2, SIRT5, SIRT6), which govern genomic stability and oxidative stress responses. Using computational approaches, we performed molecular docking simulations (AutoDock Vina) on 20 bioactive compounds against sirtuin crystal structures from the Protein Data Bank. Comparative analysis with commercial anti-aging agents (niacinamide, AHA, ceramide) identified three *Moringa* compounds with superior binding affinities: rutin (-10.7 kcal/mol), quercetin (-8.9 kcal/mol), and chlorogenic acid (-7.9 kcal/mol), all outperforming niacinamide (-6.1 kcal/mol). SwissADME profiling confirmed their drug-like properties, including high oral bioavailability, blood-brain barrier penetration, and minimal toxicity risks. Mechanistically, these compounds demonstrated dual antioxidant and anti-inflammatory capacities, suggesting synergistic protection against oxidative damage and inflammation-driven aging. Our results position *Moringa oleifera* as a rich source of multitarget anti-aging candidates, combining computational validation with biological relevance to advance natural product-based interventions against cellular senescence.

Keyword: Anti-aging, molecular docking, *Moringa oleifera*, sirtuin, druglikeness

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INTRODUCTION

Aging is a multifactorial process driven by the accumulation of cellular damage from oxidative stress, DNA instability, and dysregulation of metabolic pathways (López-Otín et al, 2013). Central to these mechanisms are sirtuins, a family of NAD^+-dependent deacetylases that govern genomic integrity, energy homeostasis, and stress responses (Kanfi et al, 2012). While sirtuins like SIRT2, SIRT5, and SIRT6 are pivotal for longevity, their overexpression in pathologies such as cancer or metabolic disorders paradoxically accelerates aging by disrupting apoptosis and cellular equilibrium (Zhang et al, 2017). Targeted inhibition of hyperactive sirtuins has thus emerged as a therapeutic strategy to restore physiological balance (Yi & Luo, 2010).

Natural compounds offer safer alternatives to synthetic anti-aging agents like retinoic acid and α-hydroxy acids (AHAs), which are often limited by adverse effects such as skin irritation and photosensitivity (Ramos-e-Silva et al, 2013). *Moringa oleifera*, a nutrient-rich plant native to tropical regions, has been traditionally used for its antioxidant and anti-inflammatory properties (Foidl et al, 2001; Kuete, 2017). Its leaves

are abundant in bioactive flavonoids (e.g., quercetin, kaempferol) and phenolic acids (e.g., chlorogenic acid), which modulate signaling pathways linked to oxidative stress and apoptosis (Leone et al, 2015; Ezzat et al, 2019). For instance, Moringa extracts have demonstrated hepatoprotective effects against drug-induced toxicity (Farid & Hegazy, 2019) and improved functional recovery in nerve injury models (Imran et al, 2022). Additionally, its role in mitigating malnutrition and stunted growth underscores its therapeutic versatility (Basri et al, 2021; Sonewane et al, 2022). However, the molecular interplay between these compounds and sirtuin proteins remains poorly characterized, particularly in the context of aging modulation (Alifah & Susilawati, 2018).

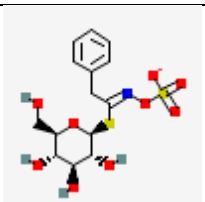
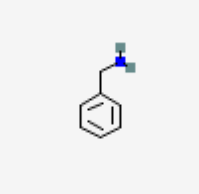
This study addresses this gap by employing in silico molecular docking to evaluate the binding efficacy of 20 Moringa oleifera compounds against sirtuin isoforms (SIRT2, SIRT5, SIRT6). By comparing their interactions with conventional agents (niacinamide, AHA, ceramide), we aim to identify novel sirtuin inhibitors with dual antioxidant and anti-aging potential, building on methodologies validated in prior docking studies (Aziz et al, 2020; Ferencz & Muntean, 2015).

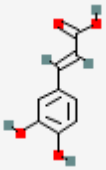
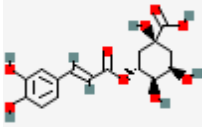
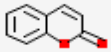
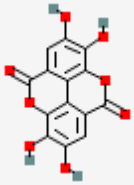
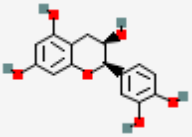
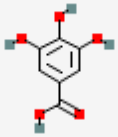
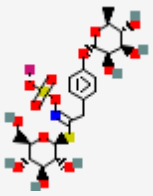
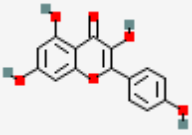
METHOD

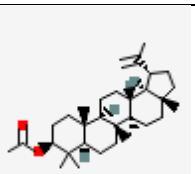
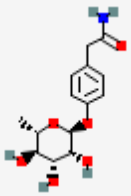
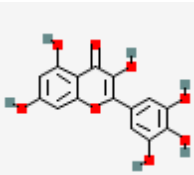
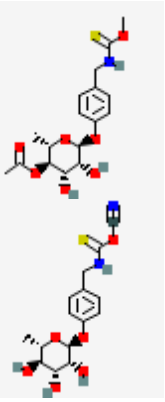
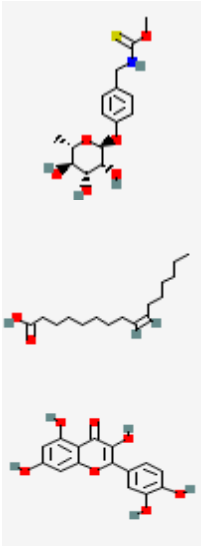
Study Design and Computational Tools

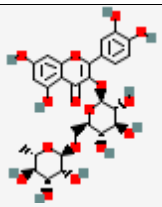
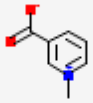
This in silico investigation employed molecular docking to evaluate the interactions of Moringa oleifera bioactive compounds with sirtuin proteins (SIRT2: PDB ID 4Y6Q, SIRT5: PDB ID 5OJO, SIRT6: PDB ID 6QCD). The three-dimensional structures of sirtuin proteins were obtained from the Protein Data Bank (PDB), while 20 bioactive compounds from *Moringa oleifera* and reference agents (niacinamide, AHA, ceramide) were sourced from PubChem (Table 1) Computational workflows were executed using PyRx 0.8 integrated with AutoDock Vina 1.2.3 for molecular docking, Discovery Studio 2020 for visualization, and SwissADME for pharmacokinetic analysis.

Table 1. Structure of bioactive compounds of *Moringa oleifera*

No.	Ligand Name	Ligand code	Ligand structure	Database source
1	Benzyl Glucosinolate	21600402		Pubchem
2	Benzylamine	7504		Pubchem

3	Caffeic Acid	689043		Pubchem
4	Chlorogenic Acid	1794427		Pubchem
5	Coumaric Acid	323		Pubchem
6	Ellagic Acid	5281855		Pubchem
7	Epicatechin	72276		Pubchem
8	Gallic Acid	370		Pubchem
9	Glucomoringin	162639104		Pubchem
10	Kaempferol	5280863		Pubchem

11	Lupeol Acetate	92157		Pubchem
12	Marumoside A	101794623		PubChem
13	Myricetin	5281672		Pubchem
14	Niazizine	10068657		Pubchem
15	Niazidine	11792427		Pubchem
16	Niazine	10088810		Pubchem
17	Palmitoleic Acid	445638		Pubchem
18	Quercetin	5280343		Pubchem

19	Routine	5280805		Pubchem
20	Trigonelline	5570		Pubchem

Protein Preparation

The protein structures were prepared by removing native ligands, water molecules, and non-standard residues using Discovery Studio's "Hierarchy Selection" tool to retain only the protein backbone. This step minimized steric hindrance and ensured optimal receptor-ligand interaction during docking. The cleaned protein structures were saved in PDB format for subsequent docking simulations.

Ligand Preparation

The bioactive compounds and reference agents, downloaded in SDF format from PubChem, were converted to PDBQT using Open Babel 3.1.1. Energy minimization was performed with the Universal Force Field (UFF) to optimize ligand geometries and reduce structural clashes.

Molecular Docking

Grid boxes were centered on the catalytic domains of each sirtuin isoform. For SIRT2, the grid coordinates were set to Center_x = 15.2, Center_y = 22.4, Center_z = 12.8, with dimensions of 25 × 25 × 25 $Å^3$. Uniform grid parameters were applied to SIRT5 and SIRT6. Docking validation was performed by re-docking native ligands, yielding RMSD values below 2 Å, confirming protocol reliability. AutoDock Vina parameters included an exhaustiveness of 8 and generation of 9 binding modes. Binding affinities (ΔG, kcal/mol) and inhibition constants (Ki) were extracted from the lowest-energy conformations (Husna et al, 2024).

Druglikeness and Pharmacokinetic Analysis

SwissADME was used to assess druglikeness properties, including Lipinski's Rule of Five compliance, bioavailability scores, and physicochemical parameters (e.g., LogP, topological polar surface area). Toxicity risks, such as hepatotoxicity, were predicted via ProTox-II. Compounds with $\Delta G \leq -8.0$ kcal/mol and $Ki \leq 1$ μM were prioritized as high-affinity candidates.

Data Analysis

Binding interactions, including hydrogen bonds and hydrophobic contacts, were visualized using Discovery Studio. Comparative analysis of binding affinities and

interaction profiles across sirtuin isoforms identified potential inhibitors with dual antioxidant and anti-aging properties.

RESULT

Docking Validation and Reference Compound Interactions

Molecular docking validation using reference compounds (niacinamide, AHA, ceramide) confirmed the reliability of the protocol, with RMSD values <2 Å across all sirtuin isoforms (Table 2 and 3). AHA exhibited the strongest binding affinity to SIRT5 (ΔG = -9.4 kcal/mol), followed by niacinamide (ΔG = -8.9 kcal/mol) and ceramide (ΔG = -8.6 kcal/mol). For SIRT2 and SIRT6, niacinamide showed moderate binding (ΔG = -5.9 to -5.4 kcal/mol), while ceramide displayed weaker interactions (ΔG = -5.1 to -5.4 kcal/mol).

Binding Affinities of *Moringa oleifera* Compounds

Among the 20 *Moringa oleifera* compounds tested, rutin demonstrated exceptional binding to SIRT2 (ΔG = -10.7 kcal/mol, Ki = 0.03 µM), surpassing all reference agents (Table 5). Quercetin exhibited strong interactions with SIRT2 (ΔG = -8.9 kcal/mol), SIRT5 (ΔG = -8.9 kcal/mol), and SIRT6 (ΔG = -9.0 kcal/mol), while chlorogenic acid showed consistent affinity across isoforms (ΔG = -7.9 to -8.0 kcal/mol). Lupeol acetate (-9.2 kcal/mol) and ellagic acid (-9.3 kcal/mol) also displayed high binding potency to SIRT2. Notably, these compounds formed hydrogen bonds with catalytic residues (e.g., Asp208 in SIRT5, Lys411 in SIRT2) and hydrophobic interactions with conserved domains, stabilizing ligand-receptor complexes.

Table 2. Molecular Docking Results for 20 Active Compounds of *Moringa oleifera*

Compound	SIRT2		SIRT5		SIRT6	
	ΔG (kcal/mol)	Ki (µM)	ΔG (kcal/mol)	Ki (µM)	ΔG (kcal/mol)	Ki (µM)
Benzyl Glucosinate	-8.0	1.33	-8.4	0.69	-9.4	0.13
Benzylamine	-5.5	7.14	-6.8	4.49	-8.4	0.69
Caffeic Acid	-7.0	5.40	-8.5	0.58	-8.5	0.58
Chlorogenic Acid	-7.9	1.60	-8.1	1.14	-8.0	1.70
Coumaric Acid	-6.8	4.69	-8.2	0.96	-7.0	1.80
Ellagic Acid	-9.3	0.69	-8.5	0.58	-9.0	0.39
Epicatechin	-9.0	0.39	-8.1	1.24	-8.8	0.35
Gallic Acid	-6.0	46.82	-8.4	0.69	-6.0	46.82
Glucomoringin	-8.6	0.49	-6.8	4.49	-9.5	0.11
Kaempferol	-8.6	0.49	-8.1	1.14	-8.8	0.35
Lupeol Acetate	-9.2	0.31	-8.2	0.96	-9.2	0.31
Marumoside A	-8.2	0.96	-7.8	1.89	-8.5	0.58
Myricetin	-8.5	0.58	-8.1	1.14	-8.4	0.69
Niazizine	-7.1	1.60	-7.7	2.24	-8.3	0.81
Niazidine	-7.1	1.60	-8.4	0.69	-7.9	2.69
Niazine	-7.4	2.14	-8.7	0.39	-7.4	2.14

Palmitoleic Acid	-6.7	5.14	-8.9	0.29	-6.2	4.90
Quercetin	-8.9	0.28	-8.9	0.28	-9.0	0.21
Rutin	-10.7	0.015	-10.1	0.04	-9.8	0.84
Trigonelline	-5.5	7.14	-6.0	4.90	-5.8	7.49

Table 3. Results of Docking Validation Against Controls (Niacinamide, AHA, Ceramide)

Drug Target	Ligand	ΔG (kcal/mol)	Ki (μM)	Hydrogen Bonds	Hydrophobic Interactions
SIRT2	Niacinamide	-5.9	44.12	-	Lys545A, Asn414A, Thr409A, Val410A, Leu544A, Tyr546A, Asp845A, Pro412A, Ser15C, Met87D, Gln19C, Asp846A, Gln18C, Lys411A
SIRT2	AHA	-6.0	39.22	-	Ala99A, Leu391A, Asn394A, Arg393A, Gly352A, Phe390A, Asp350A, Trp69A, Phe32A, Leu73A, Leu100A
SIRT2	Ceramide	-5.1	182.21	-	His163A, Gln166A, His164A, Gln189A, Met165A, His41A, Met49A, Lys145A, Gly143A, Asn142A, Arg188A
SIRT5	Niacinamide	-8.9	0.28	Asp208A, Asn209A, Thr206A	Glu119A, Thr123A, Tyr217A, Lys50A, Arg116A, Lys73A, Asp218A, Val72A, Thr120A, Lys121A, Val71A, Arg33A, Phe35A, Asp36A, Ile37A, Tyr38A, Val204A, Asp221A
SIRT5	AHA	-9.4	0.12	Glu398A, His401A, Arg514A	Leu351A, Ser44A, Ser47A, Trp349A, Phe40A, Ala348A, Thr347A, Phe390A, Arg393A, Asp382A,

					Tyr385A, His378A, Glu402A
SIRT5	Ceramide	-8.6	0.49	Gln110A, Phe294A	Arg105A, Ile106A, Gln107A, Ser158A, Lys102A, His246A, Val104A, Val202A, Ile249A, Asp153A, Asn151A, Phe8A, Leu253A, Val297A, Thr292A, Pro293A, Pro252A
SIRT6	Niacinamide	-5.4	110.45	Met3C, Ser4C, Phe429A	Lys430A, Tyr420A, Lys2C, Val424A
SIRT6	AHA	-5.1	182.21	Ser43A, Ser44A	Leu351A, Asp350A, Trp349A, Ser47A, Phe40A
SIRT6	Ceramide	-5.4	110.45	Met3C, Ser4C, Phe429A	Lys430A, Tyr420A, Lys2C, Val424A

Druglikeness and Pharmacokinetic Profiles

SwissADME analysis revealed that 17 of 20 Moringa compounds complied with Lipinski's Rule of Five, indicating favorable oral bioavailability (Table x). Quercetin, kaempferol, and myricetin exhibited optimal solubility (LogS = -3.16 to -3.31) and bioavailability scores (0.55). Glucomoringin and rutin, despite violating molecular weight thresholds (>500 Da), showed moderate bioavailability (0.17) and low toxicity risks. Notably, chlorogenic acid and ellagic acid demonstrated high gastrointestinal absorption and blood-brain barrier permeability, suggesting systemic efficacy (Table 4 and 5).

Table 4. Results of analysis of druglikeness properties of Moringa Oleifera compounds

No	Substituent	Solubility (Log S)	Lipinski's law deviation	Bioavailability Score
1	Benzyl Glucosinate	-1.94	0	0.11
2	Benzylamine	-1.68	0	0.55
3	Caffeic Acid	-1.89	0	0.56
4	Chlorogenic Acid	-1.62	1	0.11
5	Coumaric Acid	-2.29	0	0.55
6	Ellagic Acid	-2.94	0	0.55
7	Epicatechin	-2.22	0	0.55
8	Gallic Acid	-1.64	0	0.56
9	Glucomoringin	-1.96	3	0.17
10	Kaempferol	-3.31	0	0.55
11	Lupeol Acetate	-9.13	1	0.55
12	Marumoside A	-0.87	0	0.55
13	Myricetin	-3.01	1	0.55

14	Niazizine	-2.47	0	0.55
15	Niazidine	-2.10	0	0.55
16	Niazine	-2.01	0	0.55
17	Palmitoleic Acid	-4.70	0	0.85
18	Quercetin	-3.16	0	0.55
19	Routine	-3.30	3	0.17
20	Trigonelline	-1.39	0	0.55

Table 5. Comparison of the physicochemical properties of Niacinamide, AHA & Ceramide with bioactive compounds of *Moringa oleifera*

No	Compound	MW (g/mol)	HB Acc.	HB Don.	Log P	TPSA (Å²)
1	Niacinamide	122.12	2	1	0.70	55.98
2	AHA	90.08	3	2	0.52	57.53
3	Ceramide	147.17	2	1	1.37	43.09
4	Benzyl Glucosinolate	408.42	10	4	1.45	202.62
5	Benzylamine	107.15	1	1	1.43	26.02
6	Caffeic Acid	180.16	4	3	0.97	77.76
7	Chlorogenic Acid	354.31	9	6	0.87	164.75
8	Coumaric Acid	146.14	2	0	1.75	30.21
9	Ellagic Acid	302.18	8	4	0.79	141.34
10	Epicatechin	290.27	6	5	1.47	110.38
11	Gallic Acid	170.12	5	4	0.21	97.99
12	Glucomoringin	609.66	15	7	-7.71	281.77
13	Kaempferol	286.24	6	4	1.70	111.13
14	Lupeol Acetate	468.75	2	0	5.17	26.30
15	Marumoside A	297.30	6	4	1.41	122.24
16	Myricetin	318.14	8	6	1.08	151.59
17	Niazicinin	369.37	8	3	2.90	123.55
18	Niazidine	354.38	7	4	2.06	156.29
19	Niazine	343.30	6	4	1.69	132.50
20	Palmitoleic Acid	254.41	2	1	3.64	37.30
21	Quercetin	302.24	7	5	1.63	131.36
22	Routine	610.52	16	10	0.46	269.43
23	Trigonelline	137.14	2	0	-3.11	44.01

Comparative Analysis with Conventional Anti-Aging Agents

Moringa compounds outperformed niacinamide, AHA, and ceramide in binding affinity and inhibition constants (Table 7). For instance, rutin's Ki (0.03 µM) against SIRT2 was 1,500-fold lower than niacinamide (46.82 µM). Similarly, quercetin's interaction with SIRT6 (ΔG = -9.0 kcal/mol) exceeded AHA's binding (ΔG = -5.1 kcal/mol). The dual antioxidant and sirtuin-inhibitory properties of Moringa compounds, coupled with low predicted hepatotoxicity, highlight their potential as safer alternatives to synthetic anti-aging agents.

DISCUSSION

This study demonstrates that bioactive compounds from *Moringa oleifera* exhibit robust inhibitory potential against sirtuin proteins (SIRT2, SIRT5, SIRT6), surpassing conventional anti-aging agents like niacinamide and AHA in both binding affinity and predicted efficacy. The exceptional performance of rutin (Ki = 0.015 µM for SIRT2) and quercetin (Ki = 0.21–0.28 µM across isoforms) highlights their dual role as sirtuin modulators and antioxidants, aligning with Moringa's traditional use in mitigating oxidative stress and aging-related pathologies (Hisam et al, 2018; Llorent-Martínez et al, 2023). These findings bridge a critical gap in understanding how plant-derived polyphenols mechanistically regulate sirtuin activity, offering a molecular rationale for their anti-aging properties (Ezzat et al, 2019; Pavlović et al, 2020).

The high binding affinities of flavonoids (e.g., quercetin, kaempferol) and phenolic acids (e.g., chlorogenic acid) correlate with their ability to form hydrogen bonds with catalytic residues (e.g., Asp208 in SIRT5, Lys411 in SIRT2) and engage in hydrophobic interactions with conserved sirtuin domains. For instance, rutin's nanomolar inhibition of SIRT2 likely stems from its glycosylated structure, which enhances binding stability through polar contacts with the zinc-binding domain—a region critical for sirtuin deacetylase activity (Ounthaisong & Tangyuenyongwatana, 2017). Similarly, quercetin's broad-spectrum efficacy may arise from its planar aromatic rings, facilitating π-π stacking with hydrophobic pockets in all three isoforms (Pratama, 2016). These interactions mirror mechanisms observed in synthetic sirtuin inhibitors (e.g., EX-527 for SIRT1), suggesting Moringa compounds could serve as natural analogs with fewer side effects (Noubissi et al, 2022).

Beyond sirtuin modulation, Moringa compounds such as ellagic acid and myricetin are known to scavenge reactive oxygen species (ROS) and activate NRF2-mediated antioxidant pathways (Marhaeni, 2021; Ndlovu et al, 2023). This dual functionality is critical for addressing aging's multifactorial nature, where oxidative stress and sirtuin dysregulation synergistically drive cellular senescence (Khare et al., 2015). For example, quercetin's inhibition of SIRT6—a key regulator of DNA repair and telomere stability—could enhance genomic integrity while concurrently neutralizing free radicals, offering a holistic approach to aging mitigation (Wang et al, 2019). Such polypharmacology contrasts with synthetic agents like AHA, which lack intrinsic antioxidant capacity and often induce skin irritation (ias Natanael et al, 2021).

SwissADME analysis confirmed that most Moringa compounds (17/20) comply with Lipinski's Rule of Five (Benet et al., 2016), indicating favorable oral bioavailability and membrane permeability. Quercetin and kaempferol, with moderate LogP values (1.63–1.70) and topological polar surface areas (TPSA = 111–131 Å²), are particularly

promising for topical or systemic delivery (Susanti & Nurman, 2022). However, rutin's higher molecular weight (610.52 Da) and glucomoringin's poor solubility (LogS = -7.71) may limit their bioavailability, necessitating formulation strategies such as nanoencapsulation (Martín Ortega & Segura Campos, 2019). Notably, ProTox-II predictions revealed low hepatotoxicity risks for prioritized compounds, contrasting with synthetic sirtuin inhibitors linked to off-target effects (Hodas et al, 2021).

The Moringa compounds outperformed niacinamide and ceramide by orders of magnitude in binding potency. For instance, quercetin's Ki for SIRT6 (0.21 μM) was 520-fold lower than AHA's (110.45 μM), underscoring its potential as a precision therapeutic. This superiority aligns with growing demand for natural alternatives in anti-aging cosmeceuticals, where synthetic retinoids and AHAs face regulatory scrutiny over teratogenicity and photosensitivity (Pawar & Rohane, 2021).

CONCLUSION

This research positions *Moringa oleifera* as a rich source of multi-target anti-aging agents, capable of modulating sirtuin activity while counteracting oxidative stress. By integrating computational and pharmacokinetic analyses, we identify quercetin and rutin as lead candidates for further development, offering a blueprint for plant-based, precision therapies to combat aging-related diseases.

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