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ORIGINAL ARTICLE / ÖZGÜN MAKALE

IDENTIFICATION OF SIRTUIN-ACTIVATING BIOACTIVE FROM *TARAXACUM OFFICINALE* THROUGH VIRTUAL DISCOVERIES FOR ANTI-AGING AND STRESS RESISTANCE APPLICATIONS

TARAXACUM OFFICINALE'DEN SİRTUİN AKTİVE EDEN BİYOAKTİFİN ANTİ-YAŞLANMA VE STRES DİRENCİ UYGULAMALARI İÇİN SANAL KEŞİFLER YOLUYLA TANIMLANMASI

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ABSTRACT

Objective: *This study aims to investigate the interactions between sirtuins, a class of NAD+-dependent deacetylases, and bioactive ligands derived from Taraxacum officinale, focusing on their potential to modulate pathways associated with aging and stress resistance.*
Material and Method: *A comprehensive dataset of ligands was compiled from Dr. Duke's Phytochemical and Ethnobotanical Databases, and assessed for ADMETox (absorption, distribution, metabolism, excretion, and toxicity) properties using SwissADME. For virtual screening, AutoDock Vina was employed to perform molecular docking between the active sites of Sirt1-7 enzymes and a library of 51 bioactive compounds from Taraxacum officinale. Finally, BIOVIA Discovery Studio 2024 was utilized for the visualization of protein-ligand interactions.*
Result and Discussion: *The observed protein-ligand interactions highlight the potential of Taraxacum officinale bioactive compounds to modulate sirtuins, which may lead to beneficial effects on metabolic health and cellular resilience. In particular, the compounds such as taraxerol, taraxasterol, and beta-amyrin, appear in top 10 highest having strong interaction to sirtuin protein (Sirt1-7), underscore the significance of Taraxacum officinale bioactive in therapeutic strategies aimed at targeting aging and stress-related conditions. This study serves as a valuable foundation for discovering novel therapeutic agents that target sirtuins to promote healthy aging and enhance stress resilience.*
Keywords: *Anti-aging, sirtuin, stress resistance, Taraxacum officinale, virtual screening*

ÖZ

Amaç: *Bu çalışma, NAD+-bağımlı deasetilazlar sınıfı olan sirtuinler ile Taraxacum officinale'den türetilen biyolojik aktif liganlar arasındaki etkileşimleri incelemeyi amaçlamaktadır. Çalışma, bu etkileşimlerin yaşlanma ve stres direnci ile ilişkili yolları modüle etme potansiyeline odaklanmaktadır.*

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Gereç ve Yöntem: *Dr. Duke'un Fitokimyasal ve Etnobotanik Veritabanlarından bir ligan veri seti derlenmiş ve SwissADME kullanılarak ADMETox (emilim, dağılım, metabolizma, atılım ve toksisite) özellikleri açısından değerlendirilmiştir. Sanal tarama için, Sirt1-7 enzimlerinin aktif bölgeleri ile Taraxacum officinale'den elde edilen 51 biyolojik aktif bileşen kütüphanesi arasında moleküler yerleştirme yapmak üzere AutoDock Vina kullanılmıştır. Son olarak, protein-ligan etkileşimlerinin görselleştirilmesi için BIOVIA Discovery Studio 2024 kullanılmıştır.*

Sonuç ve Tartışma: *Gözlemlenen protein-ligand etkileşimleri, Taraxacum officinale biyoaktif bileşiklerinin sirtuinleri düzenleme potansiyelini vurgular ve bu da metabolik sağlık ve hücresel dayanıklılık üzerinde faydalı etkilere yol açabilir. Özellikle, taraxerol, taraxasterol ve beta-amirin gibi bileşikler, sirtuin proteini (Sirt1-7) ile güçlü etkileşime sahip en yüksek 10'da yer alır ve yaşlanma ve stresle ilişkili durumları hedeflemeyi amaçlayan terapötik stratejilerde Taraxacum officinale biyoaktifinin önemini vurgular. Bu çalışma, sağlıklı yaşlanmayı desteklemek ve stres dayanıklılığını artırmak için sirtuinleri hedefleyen yeni terapötik ajanları keşfetmek için değerli bir temel görevi görür.*

Anahtar Kelimeler: *Anti-aging, sanal tarama, sirtuin, stres direnci, Taraxacum officinale*

INTRODUCTION

Aging in humans involves complex biological changes that lead to decreased function and increased disease susceptibility due to a combination of genetic, environmental, and lifestyle factors [1]. Key mechanisms driving aging that leads to the deterioration of an organism include [2]: 1) Cellular senescence, where damaged cells become inactive and promote inflammation [3], 2) Oxidative stress, which results from an imbalance between reactive oxygen species and antioxidant defenses [4], 3) Telomere shortening, which limits the number of cell divisions [5], and 4) Mitochondrial dysfunction, which reduces energy production [6]. Understanding these complicated processes, particularly their interactions with hormones, genetics, and the immune system, is vital [7].

Chronic stress can accelerate aging by increasing inflammation, oxidative stress, and cellular damage, leading to age-related diseases such as cardiovascular issues and neurodegeneration [8]. In contrast, strong stress resistance, which characterized by effective coping mechanisms and adaptive responses, can mitigate these harmful effects, promoting cellular repair and longevity [9], thus, effective stress management and resilience critical for promoting longevity [10]. Given the critical role of these mechanisms in aging, the sirtuin family emerges as a key player in modulating these processes and enhancing cellular resilience.

The sirtuin family consists of seven mammalian proteins (SIRT1-7) that are NAD+-dependent deacetylases, playing crucial roles in various cellular processes such as histone deacetylation, metabolism regulation, oxidative stress response, and potential links to longevity [11]. SIRT1, primarily found in the nucleus, influences gene expression, cell survival, and stress response. It particularly well-known for its regulatory functions in metabolism and gene expression. SIRT1 achieves this by deacetylating lysine residues on histones and transcription factors such as p53 and NF-κB, thereby altering chromatin structure and influencing gene activity. This process is closely linked to cellular energy status, as SIRT1 activity is dependent on NAD+ availability. By enhancing fat oxidation and reducing lipogenesis through deacetylation of metabolic regulators such as PGC-1α, SIRT1 has a significant impact on metabolic pathways [12]. SIRT2 and SIRT3 also contribute to important cellular functions. SIRT2 primarily operates in the cytoplasm, where it regulates the cell cycle by deacetylating tubulin, thereby influencing microtubule dynamics and mitotic progression. In addition, it interacts with proteins associated with neurodegenerative diseases, promoting cell survival [13]. In contrast, SIRT3 is located in mitochondria and focuses on regulating mitochondrial metabolism and oxidative stress responses. SIRT3 deacetylates key mitochondrial enzymes to increase their activity, activates antioxidant enzymes such as superoxide dismutase, and promotes fatty acid oxidation, thus playing a critical role in energy metabolism and cellular health [14].

The remaining sirtuins, SIRT4 through SIRT7, also have unique functions. SIRT4, located in mitochondria, combines deacetylase and ADP-ribosyltransferase activities to regulate insulin secretion and modify protein function [15]. SIRT5 is involved in regulating metabolic pathways, increasing

enzyme activity through deacetylation and demalonylation [16]. SIRT6 and SIRT7 are important for DNA repair and ribosome biogenesis, respectively. SIRT6 maintains genomic stability through its role in the base excision repair pathway and influences glucose metabolism [17], while SIRT7 enhances protein synthesis by deacetylating ribosome assembly proteins and regulating ribosomal RNA transcription [18]. Together, these sirtuins form a complex network that modulates vital physiological processes and cellular responses to stress. Sirtuins are integral to maintaining cellular homeostasis and responding to stressors, making them potential therapeutic targets for age-related diseases and metabolic disorders [19].

The selection of sirtuins (1 to 7) as therapeutic targets, compared to other potential receptors, was based on several important criteria: their critical role in regulating important biological processes such as metabolism, aging, and cellular stress responses; their association with a variety of diseases, including neurodegenerative disorders and cancer [20]; their unique functions and substrate specificity, which allow for tailored therapeutic strategies; their proven therapeutic potential in preclinical studies; and the existence of specific inhibitors or activators that support drug research and development [21]. These considerations underscore the importance of sirtuins in health and disease, positioning them as promising candidates for targeted therapies.

Taraxacum officinale, commonly known as dandelion, has a long history of use as a traditional herbal remedy, with its diverse medicinal properties in various cultures around the world. Dandelion is recognized for its potential health benefits, including anti-inflammatory, antioxidant, and diuretic effects [22]. The roots, leaves, and flowers of dandelion are rich in bioactive compounds, such as polyphenols, triterpenes, and vitamins, which contribute to its therapeutic applications. Traditionally, dandelion has been utilized to support digestive health, enhance liver function, and promote overall well-being. It has adaptability to various environments and present widespread across Europe, Asia, and North America, and makes it a very interesting subject for modern studies of herbal therapies and their possible roles in modern healthcare [23].

This study explores the potential of *Taraxacum officinale* bioactive using virtual screening techniques to identify promising therapeutic candidates that can positively influence sirtuin activity, thereby potentially mitigating the effects of aging and chronic stress. Virtual screening techniques are an essential part of drug development, especially in targeting sirtuins, which are significant regulators in aging and stress resistance [24]. Virtual screening, by simulating the interactions between bioactive compounds and sirtuin proteins, identifies and prioritizes potential therapeutic candidates, accelerating the process of discovery [25]. This method provides insight into the mechanisms at the molecular level, increases cost-effectiveness by reducing the workload in the laboratory, and is integrated with experimental validation for confirming biological activity. Ultimately, the study aspires to contribute to the development of new strategies for enhancing longevity and improving health outcomes by targeting the sirtuin pathway through naturally derived bioactive compounds.

MATERIAL AND METHOD

System Configuration

Molecular docking was conducted using PyRx from The Scripps Research Institute, which incorporates AutoDock Vina as the docking engine [26]. Open Babel (integrated in PyRx) was used to prepared the ligand (compounds) which was imported in the form of SDF (structured data file), minimization of the energy, and convert them to PDB and further in AutoDock Vina to PDBQT format which stand for Protein Data Bank Partial Charges (Q) and Torsions (T).

The process predicted the binding affinity of *Taraxacum officinale* constituents within target proteins, with visualizations generated by Biovia Discovery Studio 2024 (Dassault Systèmes). Computations were performed on Personal Computer (PC) 11th Gen (Rocket Lake) Intel i9 processor with 8.00 GB RAM.

Ligand Structure Preparation

Three-dimensional structures of potential ligands were retrieved from the PubChem, an open chemistry database at The National Center for Biotechnology Information (NCBI), a division of the

National Library of Medicine (NLM) at the U.S. National Institutes of Health. The structures of 51 compounds were selected from a list of 280 bioactive compounds of Taraxacum officinale, taken from Dr. Duke's Phytochemical and Ethnobotanical Databases of the U.S. Department of Agriculture [27]. The selection process involves retrieving three-dimensional structures of potential ligands from PubChem. Systematic evaluation includes bioactivity, structural characteristics, and relevance to the research objectives. This careful selection aims to focus on the most promising candidates for further investigation into their therapeutic potential.

Table 1. Classification of bioactive compounds and potential biological activities

Category	Compound Name	CID	Notes
Amino Acids	Aspartic Acid	5960	Essential for neurotransmission and metabolic functions
	Glutamic Acid	33032	
Vitamins	Thiamine	1130	Plays crucial roles in metabolic processes
	Riboflavin	493570	
	Alpha-Tocopherol	14985	
Organic Acids	4-Hydroxyphenylacetic Acid	127	Antioxidant and anti-inflammatory properties
	Nicotinic Acid	938	
	Vanillic Acid	8468	
	Ferulic Acid	445858	
	p-Coumaric Acid	637542	
	Caffeic Acid	689043	
	Chlorogenic Acid	1794427	
	D-Glucuronic Acid	94715	
	2-Carboxyarabinitol	5165850	
	4-Oxopentanoate	5177120	
	L-Tartaric Acid	444305	
Sterols and Triterpenes	Beta-Sitosterol	222284	Contributes to membrane stability and signaling
	Campesterol	173183	
	Beta-Amyrin	73145	
	Taraxerol	92097	
	Cycloartenol	92110	
	Stigmasterol	5280794	
	Taraxasterol	115250	
	Faradiol	9846222	
	Arnidiol	10478550	
	Cycloartanol	12760132	
	31-Norcycloartenol	14524546	
	(+)-Taraxerol	42608290	
Flavonoids	Quercetin	5280343	Modulates oxidative stress and inflammation
	Luteolin	5280445	
	Isoquercetin	5280804	
	Luteolin 7-O-glucoside	5280637	
	Apigetrin	5280704	
	Isorhamnetin	5281654	
	Neoxanthin	5282217	
	Jasmonic Acid	5281166	
	Antheraxanthin	5281223	
	Cryptoxanthin	5281235	
	Flavoxanthin	5281238	
	Lutein	5281243	
	Lutein 5,6-epoxide	5281244	
Other Compounds	Scopoletin	5280460	Significant for health promotion
	Esculetin	5281416	
	Coumestrol	5281707	
	Quercimeritrin	5282160	
	Sitogluside	5742590	
	Androsterol	7056608	
	Germacranolide	91694425	
	Taraxacoside	131750952	
	Taraxacin	5241825	
	Violaxanthin	448438	

The classification of bioactive compounds highlights a diverse array of chemical structures, each with potential biological activities that are crucial for various physiological functions. These compounds were organized into several categories based on their chemical nature and biological roles, and divided into 6 category group as presented in Table 1. The category includes amino acids, vitamins, organic acids, sterols and triterpenes, flavonoids, and other compounds that do not belong to the previous categories. The table organizes the compounds by category, along with their CID numbers and brief notes on their significance.

The energy of the ligand structure was minimized using Open Babel with the Universal Force Field (UFF) parameters. UFF calculates the energy of a molecular system by considering various interactions, including bond stretching, angle bending, torsional (dihedral) angles, and non-bonded interactions such as van der Waals forces and electrostatics. Optimization algorithm in minimization of energy was used with 1000 number of steps. This step was essential to ensure that the ligands were in their most stable conformations prior to docking. Proper energy minimization helps improve the accuracy of subsequent docking simulations.

Sirtuin Macromolecules

This research focused on proteins associated with Sirtuin activity, crucial for regulating aging and stress resistance [28]. Sirtuin protein structures (Table 2) were retrieved from the Research Collaboratory for Structural Bioinformatic (RCSB) Protein Data Bank, prepared for docking by removing water and adding hydrogen atoms using Biovia Discovery Studio.

Table 2. Key functions of sirtuins related to aging and stress resistance

Protein Name	Function
Sirtuin 1 (PDB code: 4i5i) [29]	Involved in lifespan extension, DNA repair, and cellular senescence.
Sirtuin 2 (PDB code: 8tgp) [30]	Regulates the cell cycle.
Sirtuin 3 (PDB code: 3gls) [31]	Manages mitochondrial activity and oxidative stress; linked to longevity-associated SNPs.
Sirtuin 4 (PDB code: 5ojn) [32]	Engages in fatty acid oxidation and apoptosis.
Sirtuin 5 (PDB code: 2nyr) [33]	Contributes to fatty acid oxidation and oxidative stress management.
Sirtuin 6 (PDB code: 3k35) [34]	Supports lifespan extension, DNA repair, and telomere maintenance.
Sirtuin 7 (PDB code: 5iqz) [35]	Involved in epigenetic regulation and stress resistance.

ADMETox Prediction

ADMETox encompasses the evaluation of a compound's Absorption, Distribution, Metabolism, Excretion, and Toxicity, all critical for assessing its pharmacokinetic profile and safety in drug development. Absorption measures the compound's ability to cross biological membranes, while distribution evaluates its spread throughout the body [36]. Metabolism examines how the compound is chemically altered, affecting efficacy and safety, and excretion focuses on its elimination pathways, primarily via urine or bile. Toxicity assesses potential harmful effects on biological systems [37]. Together, these parameters provide vital insights into a drug candidate's viability and guide further development.

In-silico ADME prediction was performed using the SwissADME platform [38] to evaluate the drug-like properties of identified compounds, focusing on key pharmacokinetic parameters: absorption, distribution, metabolism, and excretion. This analysis prioritized candidates for further investigation. In addition, bioactive toxicity was predicted using ADMETlab 3.0 application developed by Computational Biology & Drug Design Group (CBDD) [39].

Lipinski's Rule of Five, one of the fundamental chemoinformatics filters for bioavailability, is central among property filters. It focuses chemical space toward drug-like narratives and avoids ADMET problems through a set of rules: (molecular weight (MW) $\leq$ 500 Da, logP $\leq$ 5, hydrogen bond donor (HBD) $\leq$ 5, hydrogen bond acceptor (HBA) $\leq$ 10, and number of rotatable bonds ($\leq$ 10) [40]. The Ghose filter identifies pharmacokinetic parameters for drug-likeness: 160 < molecular weight < 480 Da, -0.4 < logP < 5.6, 20 < number of atoms < 70 and 40 < molar refractivity < 130. The Veber filter

contains two simple rules (total polar surface area (TPSA) ≤ 140 Å2, bond rotation ≤ 10) that compounds must obey to optimize bioavailability. According to the Egan filter, compounds are likely to permeate cell membranes if they meet the following two criteria: a logP value of 5.88 or less and a topological polar surface area (TPSA) of 131.6 Å² or less [41]. Finally, Muegge's rule states that the soft mass should be less than 600 and the topological polar area should not exceed 150 [42]. Collectively, these rules guide the evaluation of a compound's drug-likeness and potential bioavailability.

Calculation of Binding Affinity

Ligand and receptor structures were imported into PyRx for molecular docking simulations using the AutoDock Vina algorithm. Parameters such as grid box (size and dimensions) and exhaustiveness (set to 8) were fine-tuned for both efficiency and accuracy in vina search space. The grid box defines the area in which ligands are allowed to dock, and refers to the 3D space around the target protein where the docking calculations are performed. The grid box is differed for each sirtuin protein (Table 3). Exhaustiveness affects the depth of the search in the conformational space, which is differ with iterations (number of optimization attempts). Higher exhaustiveness value gives more extensive search, exploring more conformations and orientations of the ligand.

Table 3. Grid box parameter of sirtuin

Sirtuin	PDB Code	Center coordinate			Dimensions (Å)		
		X	Y	Z	X	Y	Z
SIRT1	4i5i	26.59	15.43	22.69	73.94	79.68	51.05
SIRT2	8tgp	-8.16	-9.41	-6.73	37.32	56.28	59.76
SIRT3	3gls	-25.75	-25.01	20.57	140.93	106.02	100.13
SIRT4	5ojn	11.60	22.32	-14.90	48.00	42.36	63.25
SIRT5	2nyr	10.36	-15.41	11.00	58.02	66.79	66.00
SIRT6	3k35	8.54	21.69	-11.03	111.23	84.44	109.08
SIRT7	4iqz	-1.73	18.16	15.41	74.85	75.48	66.68

The resulting docking poses were assessed based on binding affinity values, with lower values indicating stronger interactions. To ensure the reliability of the docking protocol, a validation process was implemented. This involved re-docking known binders to the target protein and comparing the predicted binding modes and affinity values with previously published data [43,44].

Data Analysis and Visualization

Binding affinities of compounds derived from *Taraxacum officinale* to Sirtuin proteins were calculated in PyRx and exported in CSV format. Compounds with binding energies below a certain threshold (e.g., -7.0 kcal/mol) were considered for further analysis [45]. Values below this threshold suggest a high likelihood of significant binding affinity, making compounds more promising candidates for further biological evaluation. Interactions were visualized using Discovery Studio, offering insights into binding mechanisms and structure-activity relationships.

RESULT AND DISCUSSION

Compound Library Characterization

To explore potential therapeutic agents for Sirtuin modulation, a diverse compound library was assembled. The library comprises 51 bioactive compounds with a range of chemical structures, which is contain of 2 amino acids, 3 vitamins, 11 organic acids, 12 sterols and triterpenes, 13 flavonoids, and 10 other compounds.

Molecular weights vary from 115.11 g/mol (4-Oxopentanoate) to 600.87 g/mol (Neoxanthin), while logP values range from -3.59 (Aspartic Acid) to 7.07 (Cycloartanol), indicating diverse solubility profiles. Several compounds align with Lipinski's Rule of Five criteria, suggesting favorable

pharmacological properties, which positions the library as a promising source for new therapeutic agents aimed at Sirtuin modulation.

Bioavailability Assessment and Lipinski's Rule of Five

This study evaluated bioactive compounds from *Taraxacum officinale* for their drug-likeness properties, which are demonstrated by the SwissADME Bioavailability Radar, showing assesses key physicochemical properties essential for bioavailability: Lipophilicity, Size, Polarity, Solubility, Flexibility, and Saturation. Analysing these characteristics aids in identifying strengths and weaknesses, thereby informing the development of effective therapeutic agents. Table 4 summarizes the findings of this assessment, providing insights into the bioavailability profiles of the selected compounds.

The boiled egg model in SwissADME is a visual tool used to evaluate drug candidates' pharmacokinetic properties, specifically their ability to penetrate the blood-brain barrier (BBB) and achieve human intestinal absorption (HIA) [46]. In this model, the yolk represents compounds that can effectively cross the BBB due to their lipophilicity, while the egg white symbolizes those that are well-absorbed in the intestine. Additionally, compounds are classified based on their interaction with P-glycoprotein (PGP): PGP+ compounds are substrates that may face reduced absorption and BBB penetration, whereas PGP- compounds are less likely to interact with PGP, enhancing their bioavailability and efficacy. This model helps researchers optimize drug design for better therapeutic outcomes. Figure 1 shows ADME profile of *Taraxacum officinale* bioactive in the form of boiled-egg that shows absorption probability of the bioactive.

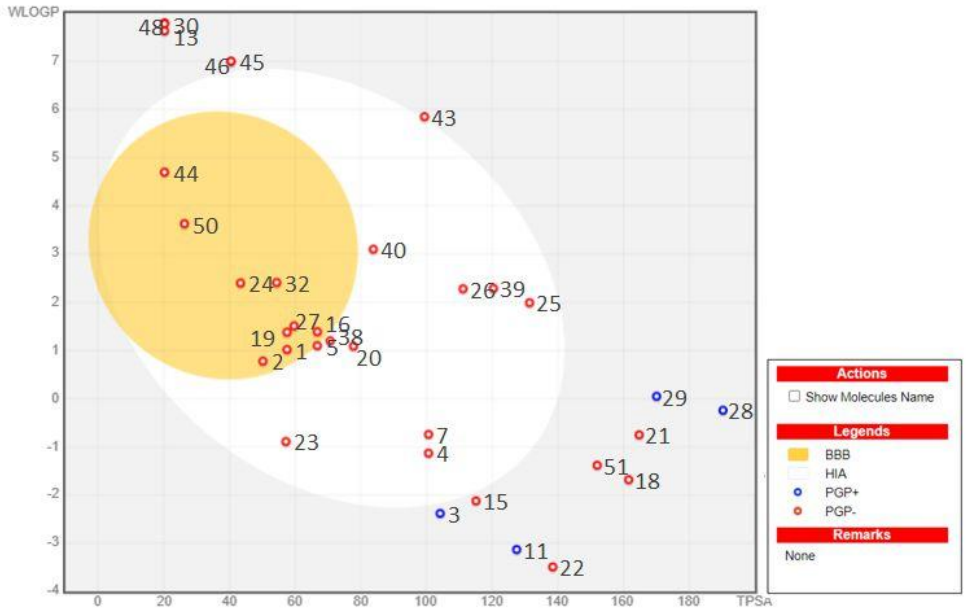
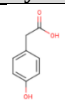
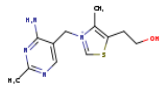
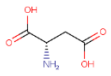
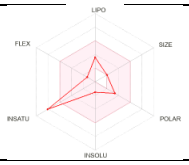
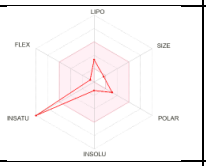
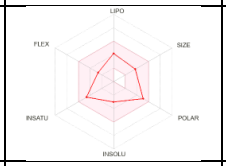
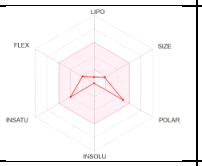
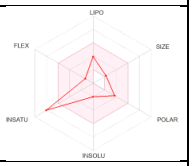
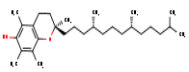
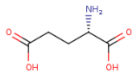
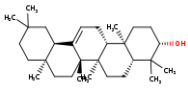
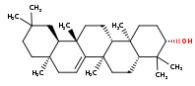
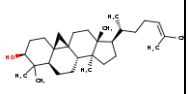
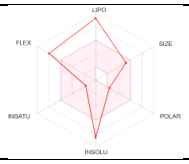
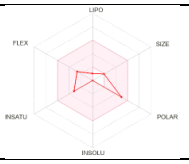
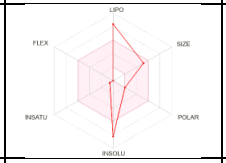
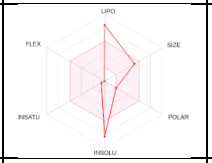
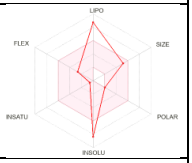


Figure 1. SwissADME Boiled-egg of *Taraxacum officinale* bioactive (Numbers represent *Taraxacum officinale* bioactive as listed in Table 4)

Table 4. Assessment of bioactive compounds for drug-likeness

No	1	2	3	4	5
Chem. Name	**4-Hydroxy-phenylacetic**	**Nicotinic acid**	**Vitamin B1**	**Aspartic Acid**	**Vanillic Acid**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**0***	**0***	**0***	**0***	**0***
Ghose #vio	**2**	**3**	**1***	**4**	**0***
Veber #vio	**0***	**0***	**0***	**0***	**0***
Egan #vio	**0***	**0***	**0***	**0***	**0***
Muegge #vio	**1***	**1***	**0***	**3**	**1***
HIA	High×	High×	Low	High×	High×
BBB perm.	Yes×	Yes×	No	No	No
Bioav. Score	0.85×	0.85×	0.55	0.56	0.85×
Hep. Tox.	Med	Med	Low°	Med	Med
Neu. Tox.	Low°	Med	Low°	Low°	Med
Geno Tox.	Med	Low°	Poor	Low°	Low°

No	6	7	8	9	10
Chem. Name	**Alpha-Tocopherol**	**Glutamic Acid**	**Beta-Amyrin**	**Taraxerol**	**Cycloartenol**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**1***	**0***	**1***	**1***	**1***
Ghose #vio	**3**	**4**	**3**	**3**	**3**
Veber #vio	**1***	**0***	**0***	**0***	**0***
Egan #vio	**1***	**0***	**1***	**1***	**1***
Muegge #vio	**1***	**2**	**2**	**2**	**2**
HIA	Low	High×	Low	Low	Low
BBB perm.	No	No	No	No	No
Bioav. Score	0.55	0.56	0.55	0.55	0.55
Hep. Tox.	Poor	Low°	Med	Med	Med
Neu. Tox.	Low°	Low°	Low°	Low°	Low°
Geno Tox.	Low°	Low°	Med	Low°	Low°

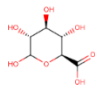
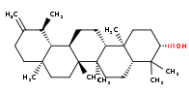
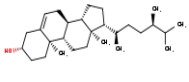
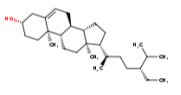
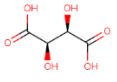
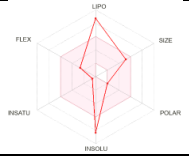
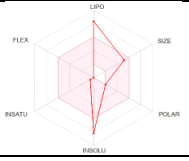
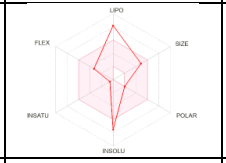
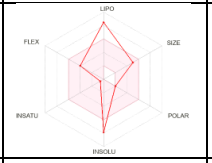
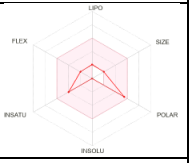
No	11	12	13	14	15
Chem. Name	**D-Glucuronic Acid**	**Taraxasterol**	**Campesterol**	**Beta-Sitosterol**	**L-Tartaric acid**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**0***	**1***	**1***	**1***	**0***
Ghose #vio	**2**	**3**	**2**	**3**	**4**

Table 4 *(continue)*. Assessment of bioactive compounds for drug-likeness

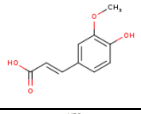
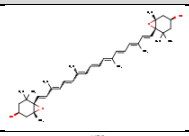
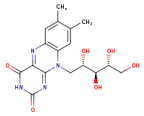
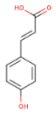
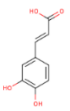
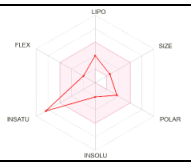
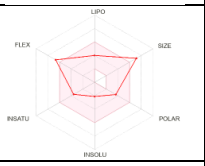
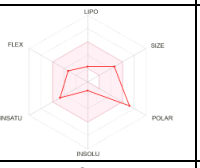
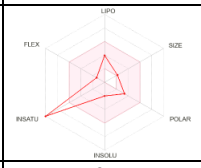
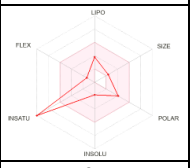
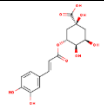
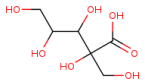
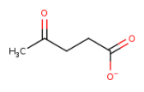
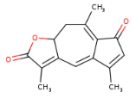
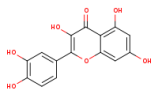
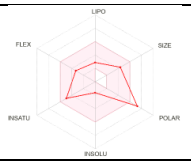
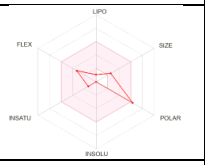
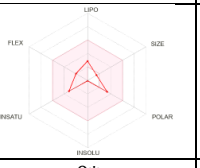
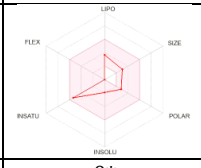
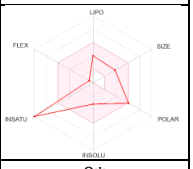
No	11	12	13	14	15
Chem. Name	**D-Glucuronic Acid**	**Taraxasterol**	**Campesterol**	**Beta-Sitosterol**	**L-Tartaric acid**
Veber #vio	**0***	**0***	**0***	**0***	**0***
Egan #vio	**0***	**1***	**1***	**1***	**0***
Muegge #vio	**2**	**2**	**2**	**2**	**2**
HIA	Low	Low	Low	Low	Low
BBB perm.	No	No	No	No	No
Bioav. Score	0.56	0.55	0.55	0.55	0.56
Hep. Tox.	Med	Med	Med	Med	Med
Neu. Tox.	Low°	Low°	Low°	Low°	Low°
Geno Tox.	Low°	Med	Low°	Low°	Low°
No	16	17	18	19	20
Chem. Name	**Ferulic acid**	**Violaxanthin**	**Riboflavin**	**p-Coumaric acid**	**Caffeic Acid**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**0***	**0***	**0***	**0***	**0***
Ghose #vio	**0***	**0***	**1***	**0***	**0***
Veber #vio	**0***	**0***	**1***	**0***	**0***
Egan #vio	**0***	**0***	**1***	**0**	**0***
Muegge #vio	**1***	**1***	**1***	**1***	**1***
HIA	High×	High×	Low	High×	High×
BBB perm.	Yes×	Yes×	No	Yes×	No
Bioav. Score	0.85×	0.85×	0.55	0.85×	0.56
Hep. Tox.	Poor	Low°	Poor	Poor	Med
Neu. Tox.	Low°	Low°	Poor	Low°	Low°
Geno Tox.	Low°	Low°	Poor	Low°	Med
No	21	22	23	24	25
Chem. Name	**Chlorogenic Acid**	**2-Carboxy-arabinitol**	**4-Oxopentanoate**	**Taraxacin**	**Quercetin**
Structure					
Bioavail-ability radar					
Lipinski #vio.	1*	1*	0*	0*	0*
Ghose #vio	**1***	**2**	**4**	**0***	**0***
Veber #vio	**1***	**0***	**0***	**0***	**0***
Egan #vio	**1***	**1***	**0***	**0***	**0***
Muegge #vio	**2**	**3**	**1***	**0***	**0***
HIA	Low	Low	High×	High×	High×
BBB perm.	No	No	No	Yes×	No
Bioav. Score	0.11	0.56	0.85×	0.55	0.55
Hep. Tox.	Med	Low°	Med	Poor	Med
Neu. Tox.	Low°	Low°	Low°	Poor	Low°
Geno Tox.	Low°	Low°	Low°	Poor	Poor

Table 4 *(continue)*. Assessment of bioactive compounds for drug-likeness

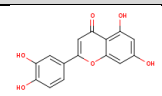
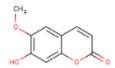
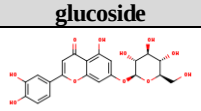
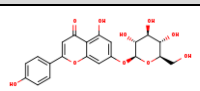
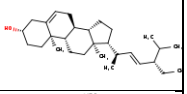
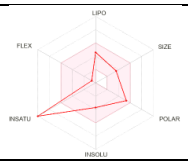
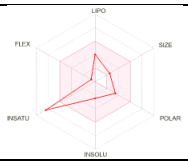
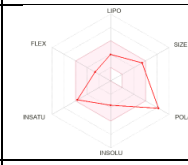
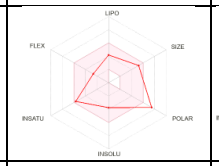
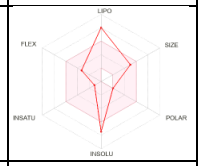
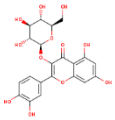
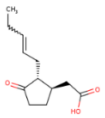
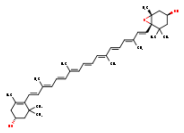
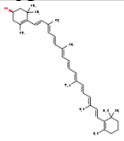
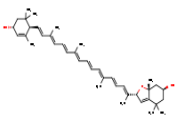
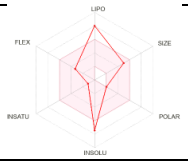
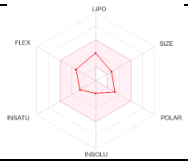
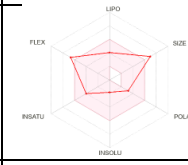
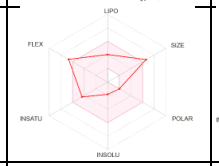
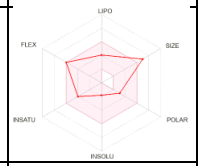
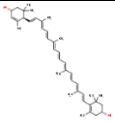
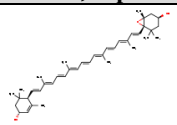
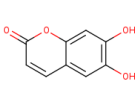
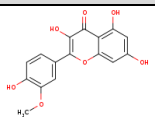
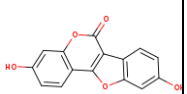
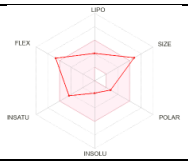
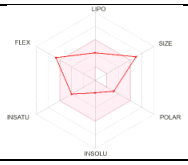
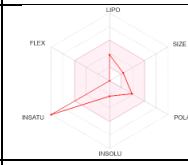
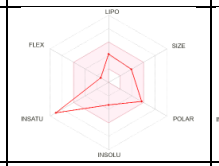
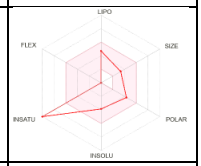
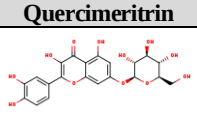
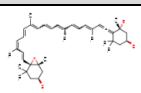
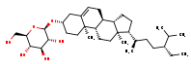
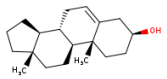
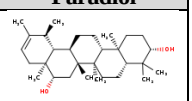
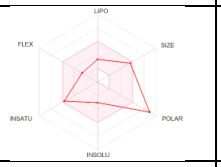
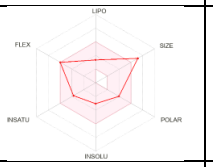
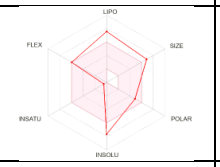
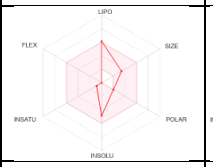
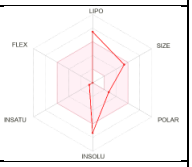
No	26	27	28	29	30
Chem. Name	**Luteolin**	**Scopoletin**	**Luteolin 7-O-glucoside**	**Apigetrin**	**Stigmasterol**
Structure					
Bioavail-ability radar					
Lipinski #vio.	0*	0*	**2**	1*	1*
Ghose #vio	**0***	**0***	**0***	**0***	**3**
Veber #vio	**0***	**0***	**1***	**1***	**0***
Egan #vio	**0***	**0***	**1***	**1***	**1***
Muegge #vio	**0***	**1***	**3**	**2**	**2**
HIA	High×	High×	Low	Low	Low
BBB perm.	No	Yes×	No	No	No
Bioav. Score	0.55	0.55	0.17	0.55	0.55
Hep. Tox.	Med	Med	Med	Med	Med
Neu. Tox.	Low°	Low°	Low°	Low°	Low°
Geno Tox.	Poor	Poor	Poor	Poor	Low°
No	31	32	33	34	35
Chem. Name	**Isoquercetin**	**Jasmonic Acid**	**Antheraxanthin**	**Cryptoxanthin**	**Flavoxanthin**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**2**	0*	0*	0*	0*
Ghose #vio	**1***	**0***	**0***	**0***	**0***
Veber #vio	**1***	**0***	**0***	**0***	**0***
Egan #vio	**1***	**0***	**0***	**0***	**0***
Muegge #vio	**3**	**0***	**0***	**0***	**0***
HIA	Low	High×	High×	High×	High×
BBB perm.	No	Yes×	Yes×	Yes×	Yes×
Bioav. Score	0.17	0.85×	0.85×	0.85×	0.85×
Hep. Tox.	Med	Med	Med	Med	Med
Neu. Tox.	Low°	Med	Med	Med	Poor
Geno Tox.	Poor	Low°	Med	Low°	Poor
No	36	37	38	39	40
Chem. Name	**Lutein**	**Lutein 5,6-epoxide**	**Esculetin**	**Isorhamnetin**	**Coumestrol**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**0***	**0***	**0***	**0***	**0***

Table 4 *(continue).* Assessment of bioactive compounds for drug-likeness

No	36	37	38	39	40
Chem. Name	**Lutein**	**Lutein 5,6-epoxide**	**Esculetin**	**Isorhamnetin**	**Coumestrol**
Ghose #vio	**0***	**0***	**1***	**0***	**0***
Veber #vio	**0***	**0***	**0***	**0***	**0***
Egan #vio	**0***	**0***	**0***	**0***	**0***
Muegge #vio	**0***	**0***	**1***	**0***	**0***
HIA	High×	High×	High×	High×	High×
BBB perm.	Yes×	Yes×	No	No	No
Bioav. Score	0.85×	0.85×	0.55	0.55	0.55
Hep. Tox.	Med	Med	Med	Med	Med
Neu. Tox.	Poor	Poor	Low°	Low°	Low°
Geno Tox.	Med	Poor	Poor	Poor	Poor

No	41	42	43	44	45
Chem. Name	**Quercimeritrin**	**Neoxanthin**	**Sitogluside**	**Androsterol**	**Faradiol**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**2**	**2**	**1***	**1***	**1***
Ghose #vio	**1***	**1***	**4**	**0***	**3**
Veber #vio	**1***	**1***	**0***	**0***	**0***
Egan #vio	**1***	**1***	**0***	**0***	**1***
Muegge #vio	**3**	**3**	**1***	**2**	**1***
HIA	Low	Low	Low	High×	Low
BBB perm.	No	No	No	Yes×	No
Bioav. Score	0.17	0.17	0.55	0.55	0.55
Hep. Tox.	Med	Med	Med	Med	Med
Neu. Tox.	Low°	Med	Low°	Low°	Low°
Geno Tox.	Poor	Med	Low°	Low°	Med

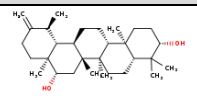
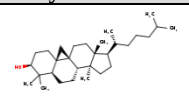
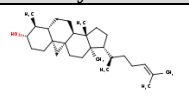
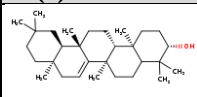
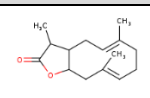
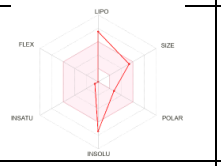
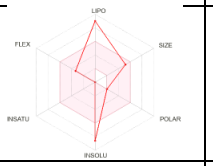
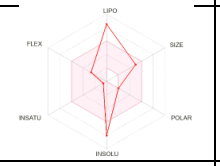
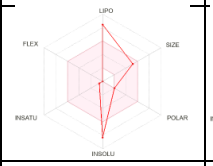
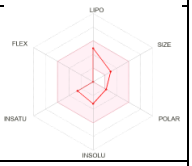
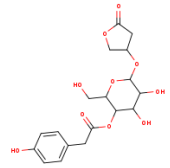
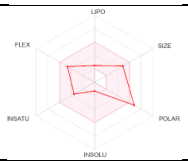
No	46	47	48	49	50
Chem. Name	**Arnidiol**	**Cycloartanol**	**31-Norcycloartenol**	**(+)-Taraxerol**	**Germacranolide**
Structure					
Bioavail-ability radar					
Lipinski #vio.	**1***	**1***	**1***	**1***	**0***
Ghose #vio	**3**	**3**	**3**	**3**	**0***
Veber #vio	**0***	**0***	**0***	**0***	**0***
Egan #vio	**1***	**1***	**1***	**1***	**0***
Muegge #vio	**1***	**2**	**2**	**2**	**0***
HIA	Low	Low	Low	Low	High×
BBB perm.	No	No	No	No	Yes×
Bioav. Score	0.55	0.55	0.55	0.55	0.55
Hep. Tox.	Med	Med	Med	Med	Med
Neu. Tox.	Low°	Low°	Low°	Low°	Med
Geno Tox.	Med	Low°	Low°	Low°	Low°

Table 4 *(continue).* Assessment of bioactive compounds for drug-likeness

No	51
Chem. Name	**Taraxacoside**
Structure	
Bioavail-ability radar	
Lipinski #vio.	**0***
Ghose #vio	**1***
Veber #vio	**1***
Egan #vio	**1***
Muegge #vio	**1***
HIA	Low
BBB perm.	No
Bioav. Score	0.55
Hep. Tox.	Poor
Neu. Tox.	Poor
Geno Tox.	Poor

Note:

1. * rule violation is preferable (0-1); ˣ bioavailability high result is preferable; bioavailability score (oral) indicator as: 0.0 – 0.3 = Low; 0.3 – 0.7 = Moderate; 0.7 – 1.0 = High; ° toxicity prefered (low value)
2. Abbreviation: #vio. = violation; HIA = Human intestine absorption; BBB = Blood-brain barrier; Bioavail.Score = Bioavailability score; Hep. Tox. = Hepatotoxicity; Neu. Tox. = Neurotoxicity; Geno. Tox. = Genotoxicity

Table 4 presents the results of drug similarity and toxicity assessments, covering several important metrics. The values highlighted in color are preferred and align with the ADMETox drug similarity rules, namely Lipinski's rule, Ghose's filter, Veber's rule, and Egan's rule, each of which evaluates drug similarity with different emphases. Lipinski's rule focuses on molecular descriptors for drug-like candidates, Ghose's filter assesses molecular descriptors relevant to drug efficacy, Veber's rule considers the number of rotatable bonds and polar surface area, and Egan's rule examines the balance of molecular properties for oral bioavailability, along with additional criteria for drug-likeness [47,48].

Intestinal Absorption (HIA) measures how well a compound is absorbed in the human gut, with higher values (typically above 30% for good absorption) indicating better absorption, which is important for oral efficacy [49]. Blood-Brain Barrier (BBB perm.) permeability is critical for central nervous system (CNS) drugs, with values above 0.3 indicating good permeability and the ability to cross this selective barrier to exert a therapeutic effect [50]. Bioavailability scores assess how effectively a drug reaches its target, with scores above 50% reflecting better absorption and overall bioavailability. Hepatotoxicity (Hep. Tox.) evaluates the potential for liver damage, with lower values (generally below 1 μM for safety) being preferred to ensure safety during drug development [51]. Neurotoxicity (Neu. Tox.) indicates the risk of toxicity to nerve cells; values should ideally be below 10 μM to minimize risk, which is critical for drugs targeting the CNS. Finally, Genotoxicity (Geno Tox.) assesses the potential for genetic damage; values indicating low genotoxicity should be below 1 for a good safety profile in drug candidates, as they help prevent mutations and cancer risk [52].

Docking Analysis of *Taraxacum officinale* Bioactive with Sirtuin

Table 5 represents the best 10 docking results, showing the binding affinities of various bioactive compounds from *Taraxacum officinale* with the sirtuin family which having higher interaction (less than -7.0 kcal/mol) [53], highlighting their potential interactions based on binding affinity. Binding free

energy, expressed in kcal/mol, quantifies the thermodynamic favorability of binding interactions; however, the term binding affinity is often used interchangeably in molecular docking studies, including in PyRx, to describe these interactions.

Table 5. Docking result (best 10) of *Taraxacum officinale* bioactive with sirtuins target showing its binding free energy (kcal/mol)

Rank	Sirtuin 1	Sirtuin 2	Sirtuin 3	Sirtuin 4	Sirtuin 5	Sirtuin 6	Sirtuin 7
1	Quercetin (-9.60)	31-Norcyclo artenol (-11.60)	Campesterol, (-10.70)	Taraxerol (-11.60)	Antheraxan-thin (-11.80)	Taraxerol (-11.50)	Beta-Amyrin (-11.50)
2	Coumestrol (-9.50)	Taraxasterol (-11.30)	(+)-Taraxe-rol (-11.00)	Taraxasterol (-11.30)	Flavoxanthin (-11.70)	Taraxasterol (-11.50)	(+)-Taraxe-rol (-11.00)
3	Apigetrin (-9.40)	Beta-Amyrin (-11.10)	Taraxerol (-10.70)	Beta-Amyrin (-11.10)	Lutein (-11.70)	Beta-Amyrin (-11.00)	Taraxerol (-10.70)
4	Flavoxanthin (-9.30)	(+)-Taraxe-rol (-11.00)	Taraxasterol (-10.70)	(+)-Taraxe-rol (-11.00)	Cryptoxan-thin (-11.40)	(+)-Taraxe-rol (-10.70)	Taraxasterol (-10.70)
5	Taraxacin (-9.20)	Faradiol (-10.90)	Cycloartanol (-10.40)	Faradiol (-10.90)	Taraxerol, (-11.00)	Faradiol (-10.30)	Cycloartanol (-10.40)
6	Chlorogenic Acid (-9.10)	Flavoxanthin (-10.70)	Cycloartenol (-9.80)	Flavoxanthin (-10.70)	Violaxanthin (-11.00)	Arnidiol (-10.30)	Cycloartenol (-9.80)
7	Germacrano lide (-9.10)	Sitogluside (-10.60)	31-Norcyclo-artenol (-9.70)	Sitogluside (-10.60)	Taraxasterol (-10.90)	Sitogluside (-10.00)	31-Norcyclo-artenol (-9.70)
8	Cryptoxan-thin (-9.00)	Cryptoxan-thin (-10.40)	Apigetrin (-9.60)	Cryptoxan-thin (-10.40)	Arnidiol (-10.90)	Apigetrin (-9.90)	Apigetrin (-9.60)
9	Isorhamnetin (-9.00)	Antheraxan-thin (-10.40)	Faradiol (-9.60)	Antheraxan-thin, (-10.40)	Faradiol (-10.80)	Campesterol (-9.90)	Faradiol (-9.60)
10	Lutein (-8.80)	Cycloartanol (-10.40)	Arnidiol (-9.60)	Cycloartanol (-10.40)	(+)-Taraxe-rol (-10.60)	Stigma-sterol (-9.90)	Arnidiol (-9.60)

Basically, all these affinities are highly important to explain the role of sirtuins in mediating the cellular action of the bioactive substances. Affinities refer to the strength of the interactions between bioactive substances and sirtuin proteins.

The sirtuins can interact with *Taraxacum officinale* bioactive ligands, although the nature of this interaction is somewhat different from that of traditional receptor-ligand binding. Unlike traditional receptors, sirtuins do not undergo conformational changes upon ligand binding; however, certain ligands can bind to the active or allosteric sites of sirtuins. This binding may enhance or inhibit the deacetylase activity of the enzymes [54]. Sirtuins contain a catalytic domain that binds NAD+ (nicotinamide adenine dinucleotide), which is essential for their enzymatic activity [55]. Additionally, they have binding sites for various small molecules, including natural compounds and synthetic drugs that can modulate sirtuin activity [56].

Analysis of Protein-Ligand Interactions

Following the docking analysis in Figure 2, the interactions between ligands (the best three bioactive from Table 5) and Sirtuin protein targets (Sirt1 to Sirt7) vary significantly for each sirtuin, which demonstrate high binding affinities and compliance with Lipinski's Rule, suggesting good oral bioavailability and therapeutic potential. Other ligands with favorable binding affinity values further indicate their promising role in modulating Sirtuin activity, warranting further investigation into their applications in anti-aging and stress resistance. The binding affinities of these ligands reflect their efficacy and specificity, with lower values suggesting more optimal interactions with key amino acid residues in the binding sites, crucial for understanding their mechanisms of action and therapeutic effects [57].

Protein-ligand interactions typically include hydrogen bonds, hydrophobic interactions, ionic bonds, and van der Waals forces. The types of interactions-such as hydrogen bonds, which stabilize binding through electrostatic attraction; hydrophobic interactions, which occur when nonpolar regions of the ligand and protein come together to avoid water; ionic bonds, which form between charged groups; and van der Waals forces, which arise from transient dipoles-contribute to the overall strength

and specificity of the binding, which ultimately influences the biological activity of the ligand [58]. The observed protein-ligand interactions indicate the potential to modulate sirtuins, influencing pathways associated with aging and stress resistance. The interaction including van der Waals and conventional hydrogen bonds, π interactions and Pi-Sigma, alkyl with carbon-hydrogen bonds, and hydrophobic interactions.

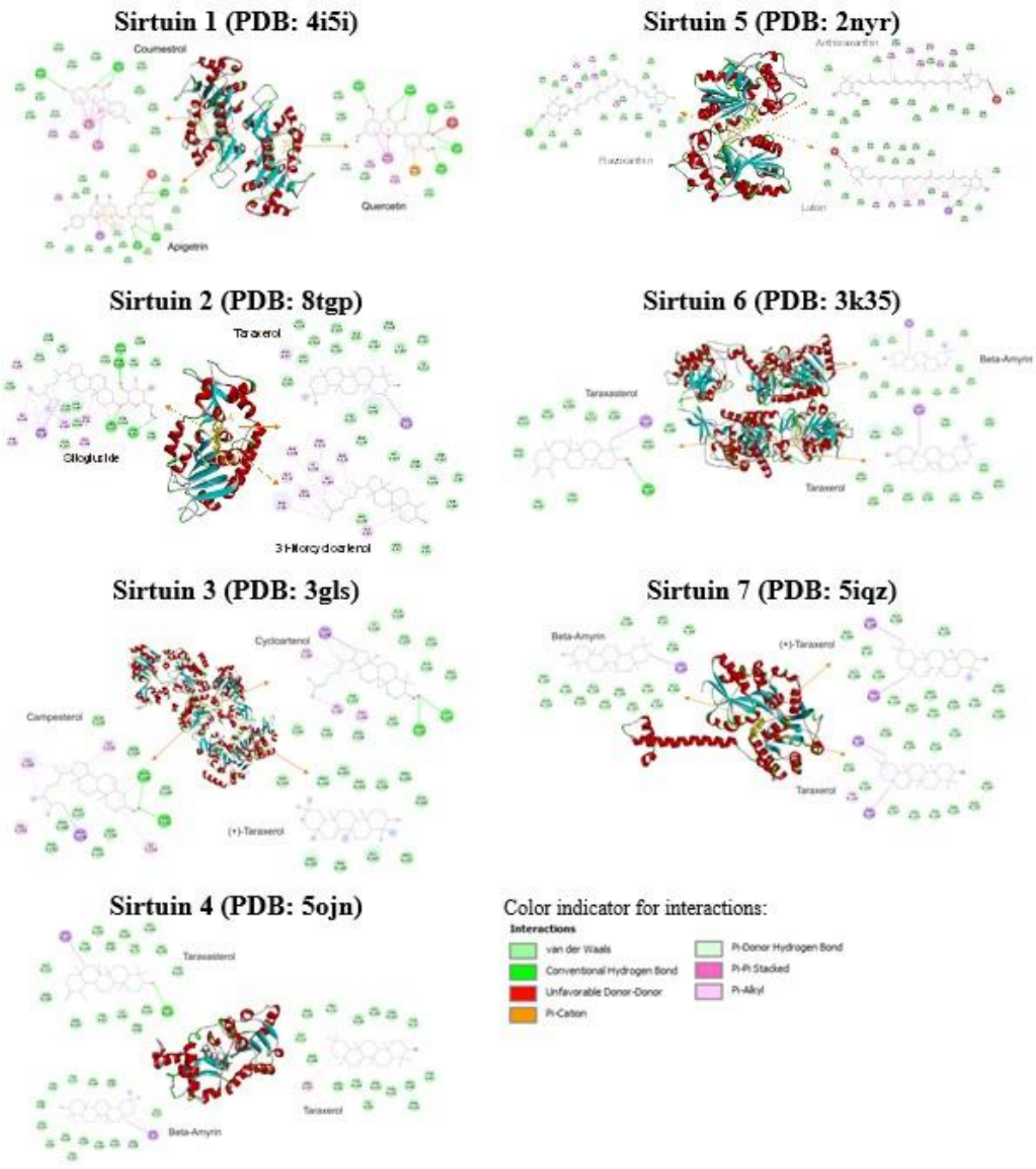


Figure 2. Visualization of Sirtuin protein – ligand interactions

Sirtuins, functioning as enzymes, are pivotal regulators within the cell, significantly influencing the acetylation state of various proteins and thereby impacting a multitude of biological processes. Their

enzymatic activities underscore their critical roles in metabolism, aging, and disease [59]. Specifically, sirtuins are integral to key processes such as: 1) metabolism and energy homeostasis, 2) cellular stress responses and survival, 3) DNA repair and maintenance of genomic stability, and 4) aging and longevity [60]. This essential involvement in vital cellular functions positions sirtuins as promising therapeutic targets for a spectrum of conditions, including metabolic disorders, neurodegenerative diseases, and age-related illnesses [61]. The findings align with these established roles, demonstrating that bioactive compounds from *Taraxacum officinale* can modulate sirtuin activity, thereby influencing metabolic pathways crucial for energy homeostasis. Specifically, compounds like taraxerol and taraxasterol exhibited favorable binding affinities with sirtuins, suggesting that they may enhance sirtuin-mediated regulation of metabolic functions. This is particularly relevant in the context of aging, where sirtuins are known to promote cellular resilience and longevity by activating stress response pathways.

Taraxerol has been shown to possess significant anti-inflammatory effects. Research indicates it can inhibit the production of pro-inflammatory cytokines and reduce inflammation in various models [62]. Taraxerol acetate was found to activate the antioxidant defense system in murine intestinal epithelial cells, effectively reducing H_2O_2-induced oxidative stress and modulating key metabolic pathways, suggesting its potential to promote health. These findings provide valuable insights for the further development of taraxerol as a therapeutic agent [63]. Taraxasterol reported has potential as an anticancer agent, with studies indicating it can inhibit the growth and proliferation of cancer cells in certain contexts, and as wound healing with its effects on certain enzyme activities [64,65]. The potential impact of these findings in the realm of anti-aging is significant; by modulating sirtuin activity, these compounds could promote improved metabolic health, enhance cellular resilience, and ultimately contribute to delayed aging and reduced risk of age-related diseases.

Beta-amyrin together with its anomer alpha-amyrin, effectively inhibited trinitrobenzene sulfonic acid-induced colitis in mice by suppressing inflammatory cytokines and COX-2 levels, likely through the inhibition of NF-κB and cAMP response element-binding protein (CREB)-signaling pathways, suggesting its potential for controlling inflammatory responses in bowel disease. This indicates that β-amyrin could be a valuable agent in managing inflammatory bowel conditions [66]. Beta-amyrin demonstrated significant anti-fibrotic effects in dimethylnitrosamine-induced hepatic fibrosis in rats by attenuating oxidative stress, inflammation, apoptosis, and fibrogenesis, suggesting its potential as a natural compound to treat liver fibrosis. These properties indicate that beta-amyrin could halt the progression of liver fibrosis to chronicity [67].

The utilization of molecular docking studies in this research has provided valuable insights into the binding free energies and ligand-target interactions of bioactive compounds from *Taraxacum officinale*. These studies reveal how effectively ligands fit into the sirtuin structure, guiding the design of novel compounds capable of modulating sirtuin activity. Notably, the ability of *Taraxacum officinale* bioactive compounds to influence sirtuin activity indicates that these ligands can significantly alter sirtuin functions, potentially affecting various biological pathways linked to aging and cellular stress responses [68]. The quantification of binding free energies further elucidates the strength of these interactions, suggesting that compounds exhibiting favorable binding profiles may enhance sirtuin activity, thereby promoting beneficial effects such as improved metabolic health and increased cellular resilience [69], although the actual binding affinity needs to determined experimentally through techniques like surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), or other biophysical methods [70].

This study highlights the promising bioactive potential of *Taraxacum officinale* as a rich source of natural compounds with significant antioxidant, anti-inflammatory, and antimicrobial properties. Particularly noteworthy are compounds like taraxerol, taraxasterol, and beta-amyrin, which rank among the top ligands for several sirtuin proteins. These compounds demonstrate the capacity to enhance cellular health and modulate sirtuin activity, making them crucial players in the processes of aging and the management of chronic diseases. Furthermore, the potential of these compounds to impact sirtuin activity may have significant implications for managing age-related diseases, including metabolic disorders and neurodegenerative conditions. By placing our findings within the broader framework of sirtuin biology, the research highlights the therapeutic potential of *Taraxacum officinale* as a source of

natural compounds that may contribute to improved health outcomes through modulation of sirtuin function.

The rich phytochemical profile of *Taraxacum officinale*, combined with its historical applications in traditional medicine, underscores its value as a candidate for further research and therapeutic development. Ultimately, this plant offers new avenues for discovering natural therapies that may improve health outcomes and enhance quality of life, particularly through the modulation of sirtuin activity and its associated biological pathways. Further research, including experimental validation and clinical studies, which include in-vitro studies: 1) to validate the target binding receptor and evaluate its binding affinity, 2) to perform cellular activity assays, including dose-response studies, mechanism of action, and cytotoxicity assays, 3) using cellular or 4) assessment of metabolic stability; or in-vivo (animal model) to assess its ADME-Tox properties, is warranted to fully explore and harness the therapeutic potential of *Taraxacum officinale* in the development of novel anti-aging strategies.

AUTHOR CONTRIBUTIONS

Concept: M.R.S., T.S.; Design: M.R.S., M.C.S.; Control: M.R.S., I.A.I.W., H.L., T.S.; Sources: M.R.S., I.A.I.W., H.L., T.S.; Materials: M.C.S.; Data Collection and/or Processing: M.R.S., T.S.; Analysis and/or Interpretation: M.R.S.; Literature Review: I.A.I.W., H.L., T.S.; Manuscript Writing: M.R.S., T.S.; Critical Review: M.R.S., I.A.I.W., H.L., T.S.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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