



Computational Identification of GPCR-Targeting Bioactive Compounds from *Ageratum conyzoides* for Anti-Aging

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Abstract

Aging is a complex biological process influenced by genetic, environmental, and lifestyle factors. Natural bioactive compounds are increasingly recognized as potential anti-aging agents. *Ageratum conyzoides* is a medicinal herb enriched with flavonoids, terpenoids, and sterols, which may contribute to its therapeutic potential. In this study, bioactive compounds derived from *Ageratum conyzoides* targeting G protein-coupled receptors (GPCRs) implicated in aging-related mechanisms were investigated using computational approaches. Molecular docking analysis was employed to evaluate forty phytochemicals against the β 2-adrenergic receptor, angiotensin II type 1 (AT1) receptor, and adenosine A2A receptor. Several compounds demonstrated strong binding affinities, including quercetin-3,7-diglucoside (−10.0 kcal/mol), friedelin (−9.0 kcal/mol), and stigmasterol (−10.3 kcal/mol). These findings suggest that *Ageratum conyzoides* contains potential ligand candidates capable of modulating G protein-coupled receptors involved in aging-related pathways. To establish biological relevance, further validation through molecular dynamics simulations and experimental studies is warranted.

Keywords:

virtual screening; molecular docking; GPCRs; *Ageratum conyzoides*; anti-aging

1. Introduction

Recent advances demonstrate that the integration of novel methodologies and advanced technologies is increasingly shaping modern medicinal chemistry. The field now recognizes computational approaches, receptor-based drug design, and natural product discovery as complementary strategies, rather than relying exclusively on conventional experimental techniques. This paradigm shift offers new opportunities for the discovery of therapeutic agents with anti-aging potential and reflects a broader trend toward enhanced efficiency and precision in the identification of bioactive compounds [1].

Virtual Screening (VS) has emerged as an important and widely adopted method in modern drug discovery,

representing a cost-effective and time-efficient alternative to conventional high-throughput screening approaches. By computationally filtering large molecular libraries, VS enables the identification of compounds with a high probability of interacting with therapeutic targets, while simultaneously excluding candidates with unfavorable physicochemical or pharmacological properties [2].

Scientists emphasize that human aging is not a simple process but rather a complex interplay of genetic predispositions, environmental influences, and lifestyle factors. Collectively, these determinants progressively contribute to the decline of physiological functions, reduced physical capacity, and increased susceptibility to disease. Several biological mechanisms contribute to this decline, including the accumulation of senescent cells that cease

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dividing but promote chronic inflammation, an imbalance between free radicals and the body's antioxidant defense systems, progressive shortening of telomeres that limits cellular regenerative capacity, and reduced mitochondrial efficiency leading to diminished energy production. Notably, these processes are not independent; rather, their interconnections—mediated through hormonal regulation, genetic factors, and immune system activity—are considered essential for explaining the mechanisms underlying aging progression [3].

Oxidative stress is widely recognized as a central contributor to the aging process. It arises when the production of reactive oxygen and nitrogen species exceeds the capacity of endogenous antioxidant defense systems, resulting in progressive damage to proteins, lipids, and other cellular components [4]. This imbalance accelerates cellular aging and contributes to age-related pathologies, including cardiovascular diseases, neurodegenerative disorders, and cancer. Other studies emphasize that aging is characterized by a decline in endogenous antioxidant defences and mitochondrial function, which collectively increases susceptibility to oxidative damage. Collectively, these findings suggest that aging is not solely a time-dependent process, but rather a biologically driven progression strongly influenced by oxidative stress. The accumulation of oxidative damage progressively compromises tissue integrity, immune function, and metabolic homeostasis, ultimately reducing physiological resilience and increasing susceptibility to chronic diseases in older adults [5].

Antioxidants play a critical role in neutralizing free radicals and maintaining redox homeostasis, thereby reducing cellular damage that contributes to accelerated functional decline. Several studies, such as Qarani et al. [6] and Meulmeester et al. [7], emphasize that enhanced antioxidant capacity is generally associated with increased resistance to degenerative changes and may contribute to the delay of aging processes. Although clinical trials have not consistently demonstrated clear therapeutic benefits, the broader body of evidence suggests that antioxidants contribute to the reduction of oxidative stress and may represent useful components in anti-aging strategies.

Ageratum conyzoides L., commonly known as Billy goat weed (Babadotan in Indonesia), is a tropical annual plant belonging to the family Asteraceae. It is widely distributed across Asia, Africa, and the Americas and is characterized by an erect, aromatic stem, opposite ovate serrated leaves, and inflorescences composed of small florets ranging in color from white to purple [8].

The ethanol extract of *Ageratum conyzoides* has been reported to contain several bioactive constituents, including flavonoids, alkaloids, tannins, and polyphenols,

which collectively contribute to its antioxidant activity and potential anti-aging effects. Although its capacity to neutralize free radicals and inhibit enzymes such as elastase and collagenase is lower than that of pure quercetin, the extract nevertheless demonstrates notable protective effects against skin aging, indicating its potential as a natural source of anti-aging agents [9,10].

G protein-coupled receptors (GPCRs) constitute the largest receptor family in the human genome, comprising approximately 800 distinct members. Structurally, they are characterized by seven transmembrane helices, enabling them to function as versatile molecular sensor [11]. These receptors can detect a diverse range of stimuli, including photons, lipids, amines, and complex proteins, and transduce them into intracellular signals that regulate a wide array of physiological processes. Upon activation, GPCRs interact with transducer proteins such as heterotrimeric G proteins, GPCR kinases (GRKs), and β -arrestins, thereby initiating multiple downstream intracellular signaling pathways [12]. Due to their widespread distribution and essential physiological roles, GPCRs have emerged as major targets in contemporary pharmacology, with therapeutic applications ranging from the treatment of cardiovascular diseases to emerging strategies aimed at modulating aging and cellular senescence [13].

Adenosine A2A receptors (A2AARs) serve as important regulators of skin fibroblast function, particularly in the modulation of extracellular matrix remodeling. Upon activation, A2AARs enhance cyclic adenosine monophosphate (cAMP) signaling, which subsequently activates downstream kinases, including ERK1/2 and p38 MAPK. These signaling pathways specifically promote the synthesis of collagen types I and III, with a relative preference for type III deposition. This selective regulation plays a critical role in tissue repair and scar formation, in which initially deposited collagen type III is subsequently remodeled into mature collagen type I. In the context of aging, diminished fibroblast activity and reduced collagen synthesis contribute to dermal degeneration and wrinkle formation. By counteracting these processes, activation of A2AARs helps restore structural integrity, elasticity, and skin hydration. Moreover, the receptor's involvement in connective tissue growth factor expression and (Wingless Protein) Wnt/ β -catenin signaling highlights its complex role in maintaining skin homeostasis. Collectively, these mechanisms underscore the rationale for targeting A2AARs through topical adenosine-based interventions, which have been reported to reduce wrinkle formation and improve skin tone in middle-aged individuals [14,15].

Another member of the GPCR family is the angiotensin II type 1 (AT1) receptor. Recent research indicates that inhibition of the AT1 receptor not only con-

tributes to blood pressure regulation and organ protection, but may also hold potential for modulating and attenuating aging-related processes. Deletion of the angiotensin AT1 receptor in mice has been reported to extend lifespan by up to 28% compared with control groups. This effect has been associated with improved cardiovascular integrity, reduced production of reactive oxygen species (ROS), decreased mitochondrial dysfunction, and increased expression of pro-survival genes, including Nampt and Sirtuin-3 (SIRT3). In contrast, in vitro exposure to angiotensin II has been shown to reduce the expression levels of both proteins. These findings suggest that activation of the angiotensin II type 1 (AT1) receptor may contribute to aging through increased oxidative stress and mitochondrial damage, whereas AT1 receptor blockade may promote lifespan extension via enhanced cellular protective mechanisms [16–18].

The β 2-adrenergic receptor (β 2AR) plays a critical role in regulating physiological functions across multiple organ systems, which undergo progressive alterations during aging. A reduced responsiveness to catecholamines, including impaired β 2AR-mediated vascular relaxation, has been observed in elderly populations. This leads to reduced vasodilation and enhanced vasoconstriction, thereby contributing to increased total peripheral resistance. Given that β 2AR is expressed on both vascular smooth muscle cells (VSMCs) and endothelial cells (ECs), diminished receptor activity directly impairs vascular responsiveness, a process that progressively declines with aging. Furthermore, reduced β 2AR activity and the consequent decline in cyclic adenosine monophosphate (cAMP) production are implicated in several aging-associated conditions, including hypertension, atherosclerosis, vascular insufficiency, and orthostatic hypotension. cAMP is known to inhibit vascular smooth muscle cell (VSMC) proliferation; therefore, diminished β -adrenergic receptor-mediated cAMP signaling may contribute to the accelerated development of restenosis and atherosclerotic progression in elderly individuals. These observations indicate that β 2AR is involved not only in the biological mechanisms underlying aging but also holds significant clinical relevance for the selection and optimization of pharmacological therapies, particularly with respect to the use of β -adrenergic receptor agonists and antagonists in older individuals [19–21].

This study aims to investigate the anti-aging potential of bioactive compounds derived from *Ageratum conyzoides* using virtual screening approaches. By employing these computational strategies, this study aims to identify promising molecular candidates capable of interacting with GPCRs, thereby providing potential therapeutic avenues for mitigating age-related changes.

2. Materials and Methods

2.1. System Configuration

The molecular docking software used in this study was PyRx 0.8 (The Scripps Research Institute), which is directly integrated with AutoDock Vina as a docking simulation engine [22]. Open Babel was employed for ligand preparation, including the import of compounds in SDF (Structure Data File) format, energy minimization of chemical structures, and conversion of file formats to PDBQT for docking analysis.

This docking process predicts the binding affinity of bioactive compounds present in *Ageratum conyzoides* toward the target proteins. The resulting protein–ligand interactions are visualized using BIOVIA Discovery Studio Visualizer (2020), enabling structural assessment of ligand–receptor binding interactions [23]. All computational procedures were performed using a personal computer (PC) equipped with an Intel Core i3-10105F processor (10th generation, Comet Lake architecture), an NVIDIA GeForce RTX 2060 graphics card with 6 GB GDDR6 memory, and 16 GB of RAM.

2.2. Ligand Preparation

The ligand profiles of *Ageratum conyzoides* were retrieved from Dr. Duke's Phytochemical and Ethnobotanical Databases maintained by the U.S. Department of Agriculture “<https://phytochem.nal.usda.gov/>” (accessed on 27 July 2025)” [24]. From the 84 bioactive constituents identified in *Ageratum conyzoides*, a total of 40 compounds were selected, as listed in Table S1. The selection was performed by excluding non-relevant molecules, including lipids, duplicate or structurally similar compounds, and those lacking complete structural information. These selected molecules were subsequently retrieved from PubChem “<https://pubchem.ncbi.nlm.nih.gov/>” (accessed on 27 July 2025)” in both 3D conformer and SDF file formats [25].

The active compounds were categorized into nine groups and are presented along with their respective PubChem CIDs in Table 1. These categories include flavonoids, phenols, terpenes, heteroorganics, olefins, terpenoids, alcohols, lipids, and phenylpropenes.

The energy of each ligand structure was minimized using Open Babel, which is integrated within PyRx 0.8, employing Universal Force Field (UFF) parameters [26]. This computational approach estimates the energy of a molecular system by accounting for multiple types of interaction terms, including bond stretching, angle

deformation, and torsional (dihedral) rotations, as well as non-covalent interactions such as van der Waals forces and electrostatic interactions. The optimization process was performed using the conjugate gradients algorithm, with a total of 1,000 steps [27]. This step is essential to ensure

that each ligand attains a stable, low-energy conformation prior to docking. Energy minimization thereby enhances the reliability and accuracy of subsequent molecular docking simulations.

Table 1: Classification of bioactive compounds.

Category	Compound Name	Chemical Formula	CID	Benefits
Flavonoids	Kaempferol	C ₁₅ H ₁₀ O ₆	5280863	Neutralize free radicals, reduce inflammation, and protect neurons
	Kaempferol-3,7-diglucoside	C ₂₇ H ₃₀ O ₁₆	6325460	
	Quercetin	C ₁₅ H ₁₀ O ₇	5280343	
	Quercetin-3,7-diglucoside	C ₂₇ H ₃₀ O ₁₇	10121947	
Phenols	Eugenol	C ₁₀ H ₁₂ O ₂	3314	Natural antioxidants
Terpenes	Bornyl Acetate	C ₁₂ H ₂₀ O ₂	93009	Anti-inflammatory often linked to stress reduction and immune balance.
	Humulene	C ₁₅ H ₂₄	5281520	
	Alpha-Cubebene	C ₁₅ H ₂₄	442359	
	Alpha-Humulene	C ₁₅ H ₂₄	24798693	
	Alpha-Murolene	C ₁₅ H ₂₄	12306047	
	Alpha-Pinene	C ₁₀ H ₁₆	6654	
	Beta-Cubebene	C ₁₅ H ₂₄	93081	
	Beta-Elemene	C ₁₅ H ₂₄	6918391	
	Beta-Farnesene	C ₁₅ H ₂₄	5281517	
	Beta-Myrcene	C ₁₀ H ₁₆	31253	
	Beta-Pinene	C ₁₀ H ₁₆	14896	
	Camphene	C ₁₀ H ₁₆	6616	
	Terpinolene	C ₁₀ H ₁₆	11463	
	Beta-Cadinene	C ₁₅ H ₂₄	10657	
	Beta-Selinene	C ₁₅ H ₂₄	442393	
	Germacrene-D	C ₁₅ H ₂₄	5317570	
	Cadinol	C ₁₅ H ₂₆ O	6428423	
	Gamma-Cadinene	C ₁₅ H ₂₄	6432404	
Heteroorganics	Demethoxyencecalin	C ₁₃ H ₁₄ O ₂	177040	Modulate enzymes, act as antioxidants and support vascular function
	Caryophyllene-Oxide	C ₁₅ H ₂₄ O	1742210	
	Coumarin	C ₉ H ₆ O ₂	323	
Olefin	Alpha-Bergamotene	C ₁₅ H ₂₄	86608	Provide antioxidant and anti-inflammatory effects
	Alpha-Terpinene	C ₁₀ H ₁₆	7462	
	Limonene	C ₁₀ H ₁₆	22311	
Terpenoids	2-Carene	C ₁₀ H ₁₆	79044	Immune defense, promote tissue repair, and act as antioxidants
	Borneol	C ₁₀ H ₁₈ O	64685	
	Friedelin	C ₃₀ H ₅₀ O	91472	

Table 1: *Cont.*

Category	Compound Name	Chemical Formula	CID	Benefits
Alcohols	Farnesol	C ₁₅ H ₂₆ O	445070	Stabilize membranes, fight microbes, and provide calming effects, supporting resilience against age-related stress.
	Linalool	C ₁₀ H ₁₈ O	6549	
	Beta-Sitosterol	C ₂₉ H ₅₀ O	222284	
	Stigmasterol	C ₂₉ H ₄₈ O	5280794	
Lipid	Linoleic Acid	C ₁₈ H ₃₂ O ₂	5280450	Essential for energy, reduce inflammation, and maintain skin integrity vital in anti-aging
	Oleic Acid	C ₁₈ H ₃₄ O ₂	445639	
	Palmitic Acid	C ₁₆ H ₃₂ O ₂	985	
Propene Phenyl	Ethyl-Eugenol	C ₁₂ H ₁₆ O ₂	6429690	Retains antioxidant

2.3. Receptors Preparation

The receptors used in this study comprised three G protein-coupled receptors (GPCRs) associated with anti-aging activity. Each receptor structure was retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank “<https://www.rcsb.org/>” (accessed on 31 August 2025). Unnecessary molecules or co-crystallized components were removed from each receptor structure using BIOVIA Discovery Studio Visualizer (2020).

Ligands and receptors were imported into PyRx for molecular docking simulations using the AutoDock Vina algorithm. To optimize both computational efficiency and docking accuracy, grid box parameters (including size and dimensions) and the exhaustiveness parameter (set to 8) were carefully defined. The grid box defines the three-dimensional search space surrounding the target protein within which ligand docking is performed and calculations are executed. Each GPCR protein included in the study was assigned a distinct grid box configuration, as summarized in [Table 2](#).

Table 2: Grid box parameters.

Receptors Name	PDB ID	Center			Dimensions (Angstrom)		
		X	Y	Z	X	Y	Z
Adenosine A2A	5G53	−28.41	1.94	16.53	138.98	124.28	78.37
β2-Adrenergic	6KR8	−4.36	2.26	−2.91	54.22	49.65	75.53
Angiotensin AT1	7F6G	124.40	104.83	152.08	91.38	88.80	115.34

3. Results

3.1. Docking Analysis

[Table 3](#) presents the docking results of 10 bioactive compounds from *Ageratum conyzoides* that exhibited moderate binding affinity values (−7.0 kcal/mol and above) toward GPCR targets. Binding affinities of ≤ −7.0 kcal/mol are generally considered indicative of strong predicted binding interactions [28]. The complete docking output files are provided in [Supplementary S1](#). Binding energy, expressed in kcal/mol, reflects the thermodynamic favorability of molecular interactions. In molecular docking studies, such as those performed using PyRx (a virtual screening tool), binding affinity is commonly used as a

metric to describe the strength and stability of ligand–receptor interactions.

Binding affinity is a critical parameter for determining the effectiveness of bioactive compounds in binding to GPCR target proteins. It reflects the strength of the interaction between the ligand and the protein at the molecular level. The docking results indicated variation in binding affinities across the three receptors, namely the adenosine A2A receptor (5G53), β2-adrenergic receptor (6KR8), and angiotensin AT1 receptor (7F6G), which may suggest their potential involvement in aging-related signalling pathways [29].

Among the evaluated compounds, stigmasterol exhibited the strongest binding affinity toward the adenosine

A2A receptor (−10.3 kcal/mol), friedelin showed notable binding affinity with the β 2-adrenergic receptor (−9.0 kcal/mol), and quercetin-3,7-diglucoside demonstrated strong binding affinity with the angiotensin II type 1 (AT1) receptor (−10.0 kcal/mol). These strong binding interactions suggest that each compound may exert se-

lective effects depending on the receptor target. Notably, stigmasterol and quercetin derivatives demonstrated consistent interactions across all three receptors with relatively high binding affinity scores, indicating their potential as multi-target ligands capable of modulating multiple GPCR-associated signaling pathways [30].

Table 3: Top 10 docking result (binding affinity kcal/mol) of *Ageratum conyzoides* bioactive with GPCRs target.

Rank	Adenosine A2A (5G53)	β 2-Adrenergic Receptor (6KR8)	Angiotensin AT1 (7F6G)
1	Stigmasterol (−10.3)	Friedelin (−9.0)	Quercetin-3,7-diglucoside (−10.0)
2	Quercetin (−9.2)	Stigmasterol (−8.6)	Kaempferol-3,7-diglucoside (−9.7)
3	Friedelin (−8.8)	Quercetin (−8.2)	Stigmasterol (−9.5)
4	Quercetin-3,7-diglucoside (−8.6)	Kaempferol (−8.1)	Quercetin (−9.2)
5	Gamma-cadinene (−8.5)	Beta-sitosterol (−8.1)	Kaempferol (−9.0)
6	Kaempferol-3,7-diglucoside (−8.4)	Cadinol (−8.0)	Beta-sitosterol (−8.7)
7	Beta-sitosterol (−7.7)	Quercetin-3,7-diglucoside (−7.8)	Friedelin (−8.0)
8	Beta-cadinene (−7.6)	Demethoxyencecalin (−7.6)	Germacrene-D (−7.8)
9	Limonene (−7.0)	Beta-cadinene (−7.5)	Beta-cubebene (−7.7)
10	Germacrene-D (−7.0)	Beta-farnesene (−7.4)	Alpha-cubebene (−7.7)

GPCRs play a central role in modulating inflammatory responses, oxidative stress, vascular tone, and cellular homeostasis, all of which are closely associated with mechanisms of aging [31,32]. The ability of these bioactive compounds to bind to such receptors suggests a promising avenue for the regulation of age-related dysfunctions [32–35]. As an illustration, flavonoids such as quercetin and kaempferol-3,7-diglucoside are well recognized for their antioxidant and anti-inflammatory properties [36,37], which may complement their receptor-binding capabilities and enhance their pharmacological relevance in anti-aging strategies.

Differences in binding affinities further reflect the distinct molecular characteristics of each compound, which are influenced by factors such as polarity, molecular size and geometry, and the capacity to form hydrogen bonds and hydrophobic interactions. These structural fea-

tures are critical in determining the binding efficiency of a compound to receptor sites and its potential to modulated own stream biological processes [30,38].

Taken together, the results provide a molecular basis for considering *Ageratum conyzoides* as a potential source of phytochemicals with anti-aging properties [9,39]. Importantly, further validation through molecular dynamics simulations, in vitro experimental studies, and pharmacokinetic analyses is required to establish the biological activity, safety profile, and therapeutic potential of these candidate compounds [40–42].

3.2. Analysis of Ligand-Protein Interactions

The ligand-protein interaction analysis was conducted to elucidate the binding behavior of bioactive compounds from *Ageratum conyzoides* with GPCR targets implicated in key aging-related pathways [9,39,43]. Docking stud-

ies demonstrated that selected phytochemicals, including stigmasterol, quercetin, friedelin, and kaempferol-3,7-diglucoside, exhibited strong binding affinities toward adenosine A2A, β 2-adrenergic, and angiotensin II type 1 (AT1) receptors [38,44,45]. These molecular interactions are defined not only by binding energy values but also by the nature of the underlying non-covalent interactions, including hydrogen bonding, hydrophobic interactions, van der Waals forces, and π - π stacking interactions [46,47].

In the case of the adenosine A2A receptor, stigmasterol and quercetin exhibited interactions with key amino acid residues, including MET270, TYR271, and LEU267, which are critical for stabilizing the ligand-receptor complex [48,49]. With regard to the β 2-adrenergic receptor (β 2AR), friedelin and stigmasterol formed hydrophobic interactions with key residues, including LEU155, VAL317, and TRP158, thereby stabilizing the ligand-receptor complex through alkyl and π -alkyl interactions [44,50]. For the angiotensin II type 1 (AT1) receptor, quercetin-3,7-diglucoside and kaempferol-3,7-diglucoside formed conventional hydrogen bonds with

key residues, including SER147, THR102, and ARG150, thereby enhancing the stability of the ligand-receptor complex and indicating their potential biological relevance [51–53].

The interaction profiles presented in Figures 1–3 provide preliminary molecular insights suggesting that these phytochemicals may potentially exert anti-aging effects via GPCR-mediated signaling pathways, although further experimental validation is required to substantiate these findings.

Stigmasterol and quercetin exhibited significant hydrophobic and π - π interactions with residues such as TYR271 and PHE168 [48,49], which are located within the transmembrane binding pocket. These interactions are potentially important, as activation of the A2A receptor is associated with collagen synthesis and the modulation of dermal fibroblast activity [54,55]. Additionally, hydrogen bonding of quercetin with GLU169 suggests a potential role in modulating receptor responses through oxidative stress-related signaling pathways, which is consistent with its well-documented antioxidant activity [56].

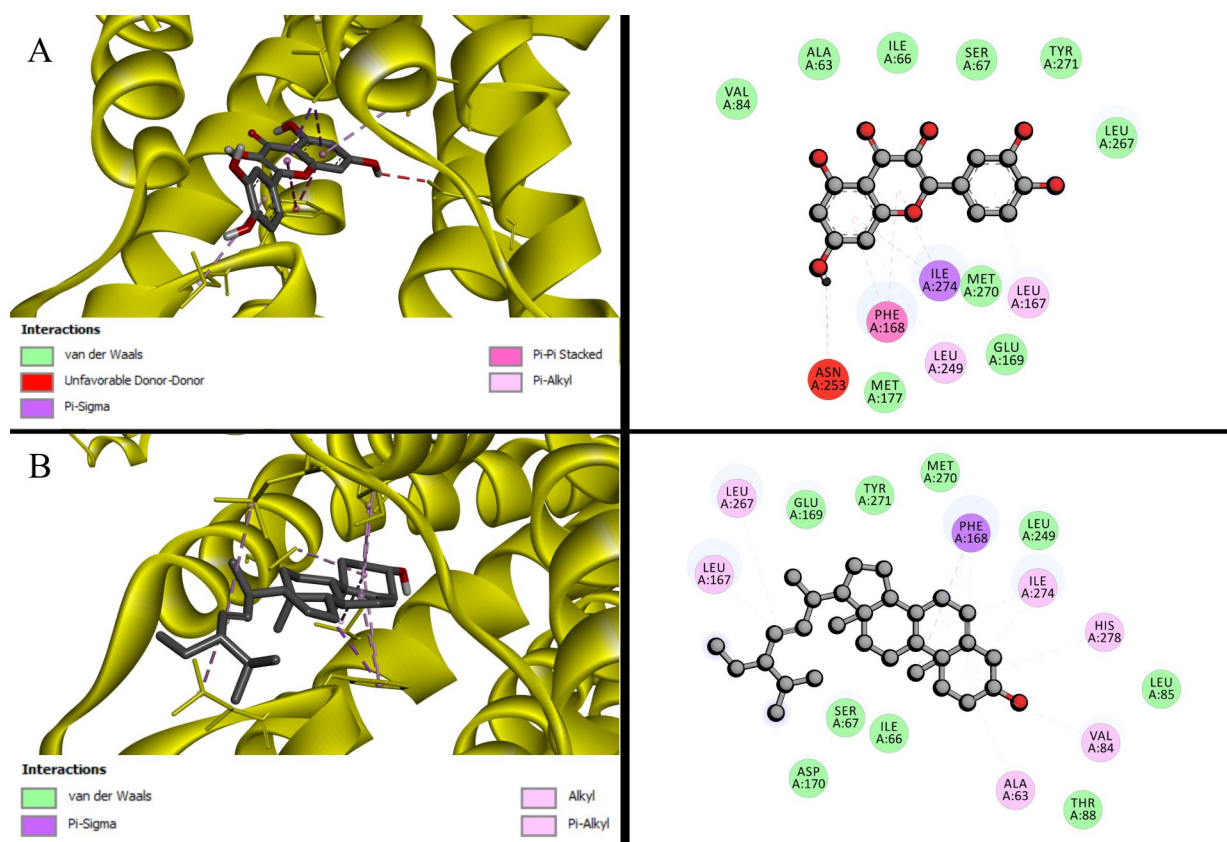


Figure 1: Adenosine A2A (5G53) interactions. (A) Quercetin, (B) Stigmasterol.

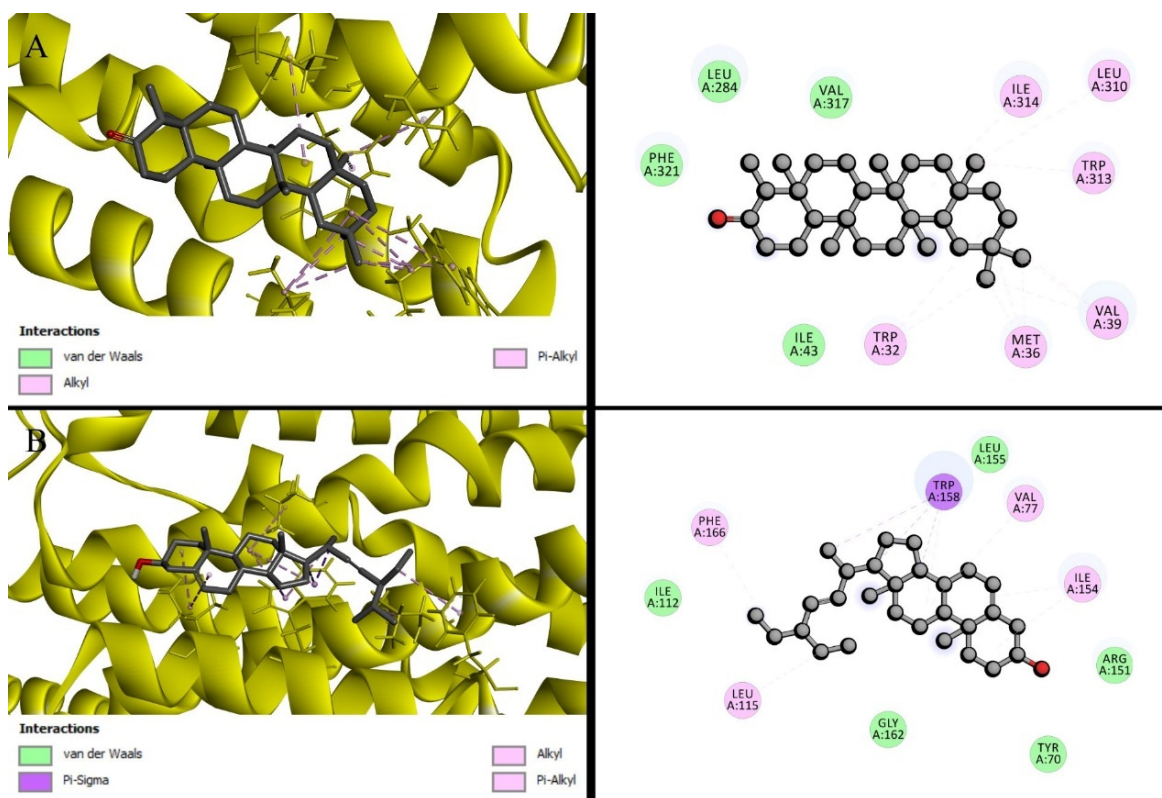


Figure 2: β 2-Adrenergic Receptor (6KR8) Interactions. (A) Friedelin, (B) Stigmasterol.

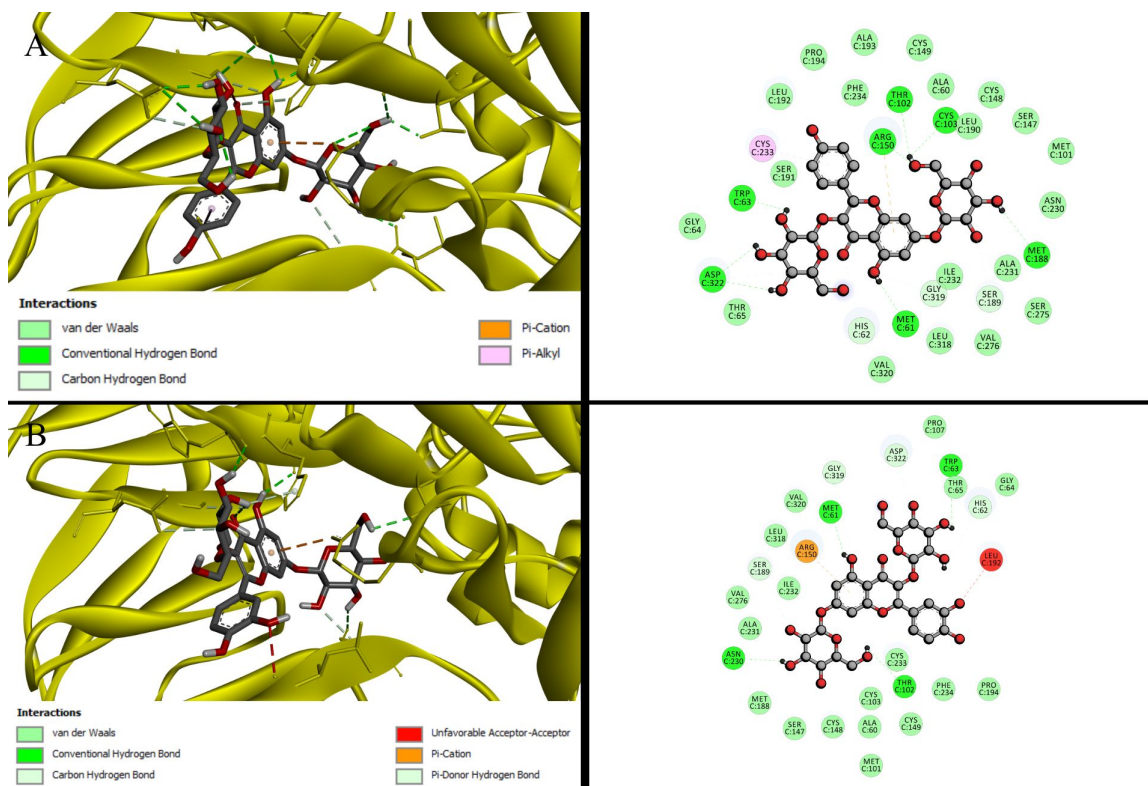


Figure 3: Angiotensin AT1—7F6G interactions. (A) Kaempferol-3,7-diglucoside, (B) Quercetin-3,7-diglucoside.

Friedelin and stigmasterol exhibited significant hydrophobic interactions with key residues, including LEU155, VAL317, and TRP158. These residues are likely critical for β 2AR-mediated vascular relaxation and regulation of the cAMP signaling pathway [57]. The stabilization of hydrophobic pockets by sterols may mitigate the age-associated decline in β 2AR responsiveness, thereby enhancing vascular tone and reducing peripheral resistance in older adults. Furthermore, π -alkyl interactions with aromatic residues such as PHE166 and TRP313 suggest that these ligands may stabilize receptor conformations essential for efficient catecholamine binding, underscoring their potential relevance in cardiovascular aging therapeutics [58].

Quercetin-3,7-diglucoside and kaempferol-3,7-diglucoside formed multiple hydrogen bonds with key amino acid residues, including SER147, THR102, and ARG150, in addition to π -cation interactions with aromatic residues. These interactions are potentially significant, as angiotensin II type 1 (AT1) receptor activation is closely associated with oxidative stress and mitochondrial dysfunctions [59]. By forming stabilizing hydrogen bonds, flavonoid glycosides may act as competitive inhibitors, attenuating angiotensin II signaling and consequently reducing reactive oxygen species (ROS) production. This observation is consistent with experimental evidence showing that AT1 receptor blockade can extend lifespan in animal models, suggesting that these natural ligands may partially mimic the pharmacological effects of AT1 antagonists [60–62].

In summary, the ligand-protein interaction analysis highlights distinct yet potentially synergistic mechanisms through which phytochemicals from *Ageratum conyzoides* may modulate GPCR activity. Sterols such as stigmasterol and friedelin primarily stabilize hydrophobic binding pockets, thereby preserving receptor conformations associated with cutaneous and vascular regulation. On the other hand, flavonoids such as quercetin and kaempferol derivatives participate in hydrogen bonding and π -cation interactions, thereby conferring antioxidant and anti-inflammatory effects while attenuating pro-aging receptor signaling pathways.

This combined mechanism of action comprising hydrophobic domain stabilization by sterols and hydrogen bond mediated regulation by flavonoids suggests a co-operative potential for multi target anti-aging therapeutic strategies [63,64]. The findings provide a molecular rationale for recognizing *Ageratum conyzoides* as a potential source of GPCR-targeting compounds with anti-aging properties. Future studies should include molecular dynamics simulations to assess binding stability, along with

in vitro and in vivo experiments to validate biological activity, safety, and pharmacokinetic applicability.

4. Discussion

This study was designed as a computational investigation focusing on virtual screening and visualization of ligand-receptor interactions. It is acknowledged that the docking protocol was not validated through redocking or RMSD analysis, which represents a limitation of the present work, particularly for GPCR targets that exhibit multiple conformational states. The absence of such validation implies that the docking scores reported herein should be interpreted with caution, as they represent only preliminary indicators of potential binding interactions rather than definitive evidence of biological activity or anti-aging effects. In addition, ADMET prediction was not performed in this study, which further represents a limitation regarding the assessment of biological relevance and translational applicability. Accordingly, the data presented in this study are intended to serve as a foundation for hypothesis generation, with future research incorporating docking validation, ADMET prediction, and experimental assays to enhance the robustness, reliability, and biological significance of the findings.

5. Conclusions

This study highlights the anti-aging potential of bioactive compounds from *Ageratum conyzoides* through in silico molecular docking approaches targeting key GPCRs, including the adenosine A2A, β 2-adrenergic, and angiotensin II type 1 (AT1) receptors. Stigmasterol, friedelin, and quercetin-3,7-diglucoside were identified as the most active ligands based on their predicted binding affinities, suggesting their potential involvement in pathways associated with collagen synthesis, vascular relaxation, and oxidative stress regulation. The consistent activity of flavonoids across multiple receptors highlights their potential role as multi target agents in addressing the complex and multifactorial nature of aging. These findings provide molecular evidence supporting *Ageratum conyzoides* as a potential natural source of GPCR-targeting compounds and underscore the utility of virtual screening as a cost-effective strategy in early-stage drug discovery. However, as the results are based solely on computational predictions, further validation through molecular dynamics simulations, in vitro and in vivo experimental studies, and pharmacokinetic analyses is required to confirm biological efficacy, safety, and therapeutic practicality. In summary, this research contributes to the growing body of literature on natural agents in anti-

aging pharmacology and offers novel perspectives for the development of multi-target therapeutic strategies.

List of Abbreviations

ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
AMP	Adenosine Monophosphate
ARG	Arginine
AT1	Angiotensin Receptor 1
cAMP	Cyclic Adenosine Monophosphate
CIDs	Compound Identifiers
DNA	Deoxyribonucleic Acid
ECs	Endothelial Cells
ERK	Extracellular Signal-Regulated Kinase
GLU	Glutamate
GPCRs	G Protein-Coupled Receptors
LEU	Leucine
MAPK	Mitogen-Activated Protein Kinase
MET	Methionine
PDB	Protein Data Bank
PHE	Phenylalanine
ROS	Reactive Oxygen Species
SDF	Structure Data File
SER	Serine
THR	Threonine
TRP	Tryptophan
TYR	Tyrosine
VAL	Valine
VS	Virtual Screening
VSMCs	Vascular Smooth Muscle Cells
β 2AR	Beta-Adrenergic Receptor 2

Author Contributions

Conceptualization, methodology, software, investigation, data curation, formal analysis, visualization, writing original draft preparation: W.Y.; Supervision, writing—review & editing: M.R.S., T.S. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

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Supplementary Materials

Supplementary material associated with this article has been published online and is available at: <https://doi.org/10.69709/MolModC.2026.101237>.

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