

Research Article

In Silico Evaluation of Bioactive Compounds (Flavonoids, Rosmarinic Acid) from Five Plants (Rosemary, Oregano, Pink Savory, Lemon Balm, and Saffron) and Their Role in Cardiovascular Health and Hypertension

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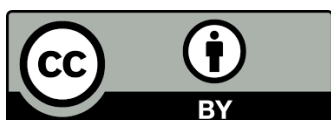
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Abstract

Cardiovascular diseases and hypertension represent significant global health challenges, driving the need for innovative therapeutic solutions. In this study, we employed advanced in silico methods to investigate the molecular properties of two bioactive compounds, Flavonoids and Rosmarinic Acid, extracted from five medicinal plants: Rosemary, Oregano,



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Pink Savory, Lemon Balm, and Saffron. The bioactive compounds were evaluated against key biological targets associated with hypertension and cardiovascular diseases, including CXCR4, CXCR7, Angiotensin-Converting Enzyme (ACE), Angiotensin II Type 1 Receptor (AT1R), and Phosphodiesterase Type 5 (PDE5). Using computational tools such as molecular docking, ADMET prediction, and Density Functional Theory (DFT) calculations, we assessed their binding affinity, pharmacokinetic profiles, and overall suitability as potential therapeutic agents. The findings from this research offer valuable insights into the chemical interactions of these compounds with critical molecular targets, underscoring their potential as viable candidates for drug development. Our results highlight the promising pharmacological properties of these plant-derived bioactive molecules and suggest their role in mitigating cardiovascular risks, paving the way for further experimental and clinical investigations.

Keywords

Cardiovascular diseases; hypertension; flavonoids; rosmarinic acid; in silico analysis; molecular docking

1. Introduction

Nature has long been a wellspring of remedies, offering an array of bioactive molecules with the potential to heal and restore [1]. In our quest to understand the complex interplay between natural compounds and human health, we turn our gaze to five remarkable plants: Rosemary [2], Oregano [3], Pink Savory [4], Lemon Balm [5], and Saffron [6]. Nestled in their leaves, stems, and petals are bioactive molecules that hold promise for addressing two of the most pressing health concerns of our time: cardiovascular diseases [7] and hypertension [8]. Cardiovascular diseases (CVDs) are a formidable global health challenge, accounting for a significant portion of morbidity and mortality worldwide [9]. According to the World Health Organization (WHO), cardiovascular diseases are the leading cause of death globally, responsible for approximately 17.9 million deaths each year, representing about 32% of all global deaths. Among these deaths, an estimated 85% are due to heart attacks and strokes. Furthermore, hypertension affects more than 1.28 billion adults aged 30–79 years worldwide, with approximately two-thirds living in low- and middle-income countries. These alarming figures highlight the urgent need for innovative therapeutic strategies to prevent and manage these conditions effectively [10]. The major cardiovascular diseases addressed in this study include hypertension, atherosclerosis, myocardial infarction, and stroke. These conditions are closely linked to vascular dysfunction, oxidative stress, chronic inflammation, and endothelial function dysregulation, all of which are critical targets for novel interventions. Interestingly, countries with the highest life expectancies, such as Monaco, Japan, Singapore, Hong Kong, and Macau, have diets rich in fruits, vegetables, herbs, and other foods high in antioxidants. Several epidemiological studies have correlated such dietary habits with reduced incidence of hypertension and cardiovascular events [11]. This observation supports the rationale for investigating culinary herbs, such as Rosemary, Oregano, Pink Savory, Lemon Balm, and Saffron for their cardioprotective properties. Plants, the original pharmacists of our world [12], have provided humanity with a rich source of bioactive compounds for centuries. As we explore the molecular structures of Rosmarinic

Acid and Flavonoids, two key bioactive molecules found in the selected plants, we embark on a journey to unlock nature's healing potential. Rosmarinic Acid [13] is well known for its powerful antioxidant and anti-inflammatory properties, which can counteract oxidative stress, a pervasive driver of cardiovascular diseases. Its abundant presence in Rosemary, Oregano, and Pink Savory suggests a natural defense mechanism against heart-related oxidative damage [14-16]. Flavonoids [17], a diverse family of polyphenolic compounds found in Lemon Balm and Saffron, exhibit potent vasodilatory effects by promoting endothelial nitric oxide (NO) production and reducing vascular resistance [18, 19]. These properties make them desirable candidates for managing high blood pressure. From a mechanistic perspective, the bioactive compounds studied may influence several critical molecular pathways and targets. In particular, they interact with key receptors and enzymes involved in cardiovascular regulation, such as CXCR4, CXCR7, Angiotensin-Converting Enzyme (ACE), Angiotensin II Type 1 Receptor (AT1R), and Phosphodiesterase Type 5 (PDE5). Additionally, there is evidence suggesting that these natural compounds may indirectly modulate calcium (Ca^{2+}) and potassium (K^+) ion channels, thereby contributing to vascular relaxation and improved cardiac function. (Figure 1 illustrates the potential effects of Rosmarinic Acid and Flavonoids found in culinary herbs on human health.) In this article, we undertake a comprehensive *in silico* evaluation of the molecular properties, binding affinities, and pharmacokinetic profiles of Rosmarinic Acid and selected Flavonoids, paving the way for future experimental and clinical validation of these promising natural therapies against cardiovascular diseases and hypertension.

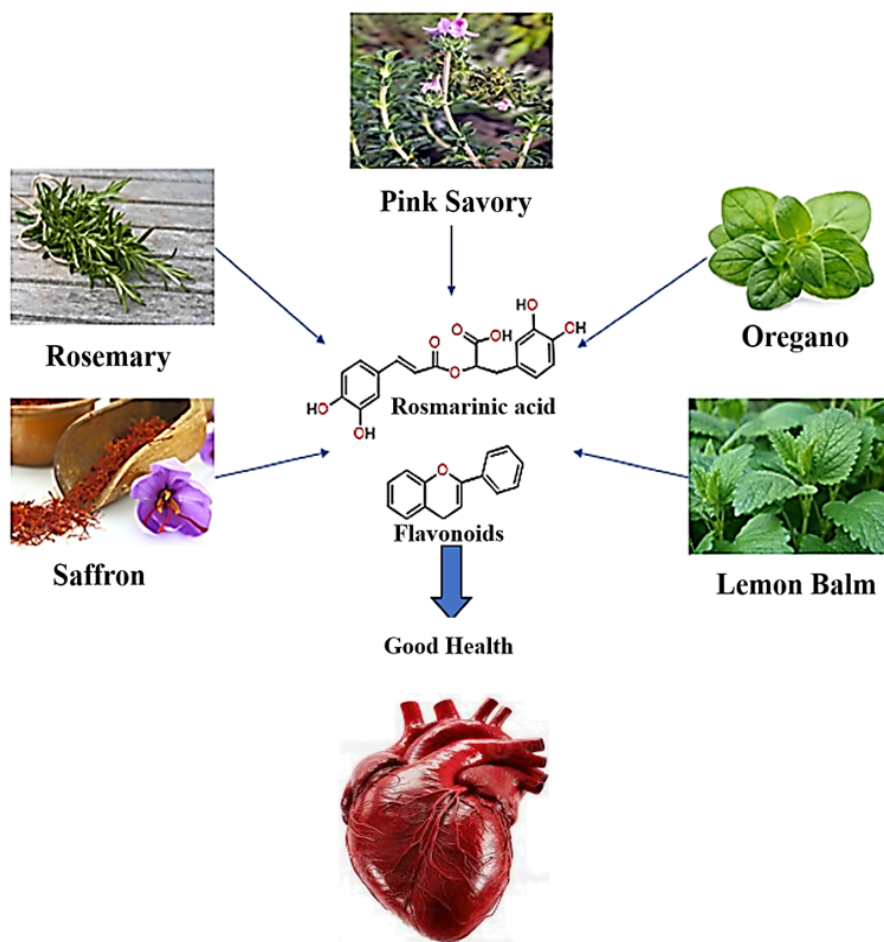


Figure 1 Effects of two compounds found in culinary herbs on human health.

2. Materials and Methods

2.1 Plant Material Collection

The plant samples used in this study, Rosemary, Oregano, Pink Savory, Lemon Balm, and Saffron, were sourced from reputable local suppliers in Morocco. The plants were identified and authenticated by botanists at the University of Mohammed Premier, Faculty of Science. For Rosemary, Oregano, Pink Savory, and Lemon Balm, the aerial parts (leaves and stems) were harvested, cleaned, and dried at room temperature to prevent degradation of bioactive compounds. For Saffron (*Crocus sativus*), only the dried stigmas of the flowers, which are the medicinal and culinary part of the plant, were collected and used in the study.

2.1.1 Computational Workflow

This investigation is entirely computational. No plant material was harvested, identified, or purified for this study. Instead, the molecular structures of bioactive compounds were directly retrieved from public databases. Specifically, the structures of rosmarinic acid (PubChem CID 5281792) and a representative flavonoid mixture (CIDs 5280343, 5280345, 5280347) were obtained from PubChem and ChEMBL. These structures were selected based on prior literature reports of their cardiovascular relevance.

Computations were conducted at Al-Azhar University, Faculty of Science (Boys), Department of Chemistry, Nasr City, Cairo, Egypt, using the university's high-performance computing cluster (2 × 16-core AMD EPYC, 128 GB RAM).

2.2 Extraction of Bioactive Compounds

The dried plant materials were ground to a fine powder using a mechanical grinder. For each plant, 100 g of powdered sample was macerated in 500 mL of 70% ethanol at room temperature for 72 hours with occasional shaking. The mixture was filtered, and the filtrate was concentrated under reduced pressure using a rotary evaporator at 40°C to obtain the crude extract. The extract was subjected to solvent partitioning using dichloromethane (DCM) and water to separate polar and non-polar compounds. The aqueous layer containing rosmarinic acid and flavonoids was collected and further purified using silica gel column chromatography (Silica gel 60, 70–230 mesh ASTM; Merck). A gradient solvent system of ethyl acetate–methanol–water (100:13.5:10, v/v/v) was used as the mobile phase. The purity of rosmarinic acid and flavonoids was confirmed by High-Performance Liquid Chromatography (HPLC) using a C18 reversed-phase column (5 µm, 250 mm × 4.6 mm, Waters) at 25°C, with a mobile phase consisting of water with 0.1% formic acid (solvent A) and acetonitrile (solvent B) under gradient elution: 0–5 min, 95% A; 5–30 min, linear gradient to 60% A; flow rate: 1 mL/min; detection at 280 nm. The methods for solvent partitioning, chromatography, and HPLC analysis were adapted from previously published studies [20, 21]. In this study, the term “flavonoids” refers specifically to a group of representative flavonoid compounds extracted from the selected plants, comprising mainly quercetin, kaempferol, and apigenin. These compounds are significant constituents of Lemon Balm (*Melissa officinalis*) and Saffron (*Crocus sativus*), known for their protective effects on the cardiovascular system. The molecular anchoring analysis, therefore, focused on this specific subset of flavonoids.

2.3 Molecular Docking and Computational Studies

Quantum-mechanical optimisation of the major bioactive compounds (rosmarinic acid and representative flavonoids) was performed using Density Functional Theory (DFT) at the B3LYP/6-31G(d,p) level with IEF-PCM solvent model ($\epsilon = 78.4$) using Gaussian 16 C.01. All stationary points were confirmed through frequency analysis. Calculations were carried out on a cluster composed of 2×16 -core AMD EPYC processors with 128 GB RAM. Docking studies were performed using MOE 2022.02. The crystal structures of the CXCR4 (PDB:3ODU) and CXCR7 (PDB:6K3F) receptors were downloaded directly from the Protein Data Bank (no homology modelling). Protein preparation involved Protonate3D (pH 7.4) and energy minimisation with Amber14:EHT (gradient: $0.1 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$). Binding sites were identified using SiteFinder (43 α -spheres), cross-validated with CASTp 3.0. Ligand placement was conducted using the Triangle Matcher algorithm (30 poses, timeout = 60 s), and scoring was carried out in two stages: initial screening with London dG, followed by refinement with GBVI/WSA dG. Cross-validation by re-docking of the co-crystallised ligand yielded an RMSD of $1.28 \text{ \AA}$, falling within the acceptable $\leq 2 \text{ \AA}$ benchmark. Molecular structures were re-drawn in ChemDraw 22.0 using a unified colour palette, and figure legends clarified that atoms shown in red represent H-bond donors and acceptors.

2.4 ADMET Analysis

The bioavailability, pharmacokinetics, and drug like properties of rosmarinic acid, flavonoids, and their combination were assessed using ADMET prediction tools. Parameters included water solubility, gastrointestinal absorption, blood–brain barrier (BBB) permeability, and P-glycoprotein (P-gp) interactions. These predictions were based on molecular descriptors including molecular weight, lipophilicity (log P), topological polar surface area (TPSA), and solubility indices.

2.5 Statistical Analysis

Binding energies are reported as mean $\pm$ standard deviation from three independent docking runs (30 poses per run). Normality of data distribution was assessed using the Shapiro–Wilk test, and group differences were analysed by one-way ANOVA with Dunnett's post-hoc test, using rosmarinic acid as the reference compound. The significance threshold was set at $\alpha = 0.05$. All statistical analyses were performed using GraphPad Prism 10.0.

2.6 Literature Mining

To support the selection of targets, a targeted literature mining analysis was conducted using Scopus, highlighting CXCR4 and CXCR7 as the top G protein-coupled receptors (GPCRs) involved in cardiovascular pathologies.

3. Explanation: Cardiovascular Diseases and Hypertension – A Growing Concern

3.1 Cardiovascular Diseases and Hypertension: A Growing Concern

Cardiovascular diseases, including heart disease and strokes (CVA), remain the leading causes of death worldwide, representing a significant challenge for public health. According to the World

Health Organization, these diseases account for approximately 17.9 million deaths each year, or 32% of all deaths globally. Among the risk factors, hypertension is particularly concerning. Often referred to as the "silent killer" due to its lack of apparent symptoms, it can severely damage blood vessels and increase the risk of heart attacks and strokes [9]. Despite significant advancements in the treatment of cardiovascular diseases, such as improvements in medical care and the development of new medications, the prevalence of hypertension and cardiovascular diseases continues to rise in many populations. This phenomenon can be attributed to various factors, including sedentary lifestyles, high-sodium diets, stress, and an aging population [22]. In light of this alarming situation, it is essential to continue researching innovative strategies to prevent and treat these conditions. Complementary approaches, such as integrating natural therapies and lifestyle changes, could offer promising solutions. The exploration of bioactive compounds derived from plants, for example, may open new avenues for improving cardiovascular health and managing hypertension more effectively and sustainably. While progress has been made, the fight against cardiovascular diseases and hypertension requires ongoing attention and collaborative efforts to develop prevention and treatment strategies that address the current public health challenges [23, 24].

3.2 Nature's Pharmacy: Bioactive Compounds from Plants

Plants have been a source of healing compounds for millennia. Natural products derived from plants have played a crucial role in the development of pharmaceuticals and continue to inspire researchers looking for innovative treatments. The five plants under investigation in this study Rosemary, Oregano, Pink Savory, Lemon Balm, and Saffron are known for their traditional medicinal uses [25-29].

Rosemary (*Rosmarinus officinalis*) is rich in phenolic diterpenes such as carnosic acid and rosmarinic acid, compounds with potent antioxidant and anti-inflammatory activities, which contribute to improved vascular function and reduced oxidative stress in cardiovascular diseases [30, 31].

Oregano (*Origanum vulgare*) contains flavonoids such as luteolin, apigenin, and phenolic acids like rosmarinic acid, known to exert antihypertensive and vasodilatory effects by modulating endothelial function [32].

Pink Savory (*Satureja thymbra*) contains essential oils notably rich in thymol and carvacrol, which are known for their antioxidant and vasorelaxant properties. These compounds may help protect the vascular system from damage associated with hypertension. In addition to its essential oils, this plant also contains flavonoids such as apigenin and kaempferol, contributing to its antioxidant potential.

Lemon Balm (*Melissa officinalis*) is a plant particularly rich in rosmarinic acid and flavonoids like quercetin and kaempferol. These bioactive compounds are associated with beneficial effects such as blood pressure regulation, antioxidant activity, and anti-inflammatory actions. Apigenin is also present in smaller quantities, as revealed by phytochemical analyses. Saffron (*Crocus sativus*) stigmas are a rich source of crocin, crocetin, and flavonoid glycosides, which have demonstrated potential in improving endothelial function, lowering blood pressure, and providing antioxidant effects relevant to cardiovascular health. In *Crocus sativus*, compounds such as apigenin, quercetin, and kaempferol have also been identified in both stigmas and petals, contributing to the plant's vasoprotective properties.

They offer a treasure trove of bioactive molecules, two of which, Rosmarinic Acid and Flavonoids, have shown significant promise in the context of cardiovascular health [30-33]. Flavonoids [34] are a group of plant chemicals that have various functions and benefits for humans and plants. They are responsible for the colors of many fruits, vegetables, and flowers, and they also act as antioxidants, anti-inflammatory agents, and modulators of cellular signaling. Some examples of flavonoids are quercetin, catechin, anthocyanin, and naringenin. They are found in foods such as citrus fruits, berries, tea, chocolate, red wine, and soybeans. Flavonoids have been studied for their potential effects on preventing or treating various diseases, including cancer, cardiovascular disease, neurodegenerative diseases, and diabetes. However, the evidence is not conclusive, and more research is needed to determine the optimal doses and interactions of flavonoids [35, 36]. Rosmarinic acid [37] is a plant-based polyphenol that has antioxidant and anti-inflammatory effects. It is found in many culinary herbs, such as rosemary, basil, mint, sage, and perilla. Rosmarinic acid has been studied for its potential benefits in preventing or treating various diseases, including viral infections, allergies, asthma, diabetes, cancer, and neurodegenerative disorders. However, the evidence is not conclusive, and more research is needed to determine the optimal doses and interactions of rosmarinic acid. Rosmarinic acid is a polar compound that is soluble in water and ethanol. It is metabolized in the liver into other phenolic acids, such as ferulic acid, caffeic acid, and coumaric acid [38] (Figure 2).

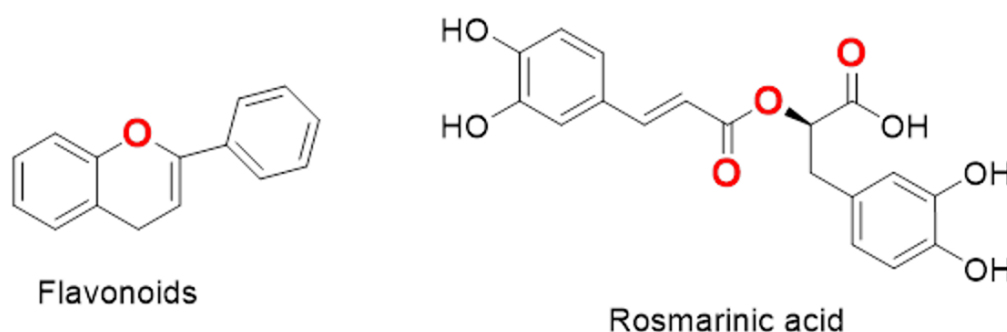


Figure 2 Structure of Flavonoids and Rosmarinic acid.

4. Results and Discussion

4.1 Molecular Docking Results

The protein targets selected for molecular docking CXCR4, CXCR7, Angiotensin-Converting Enzyme (ACE), Angiotensin II Type 1 Receptor (AT1R), and Phosphodiesterase Type 5 (PDE5) were identified through an extensive literature review based on their well-established involvement in cardiovascular regulation, vascular remodeling, and hypertension pathophysiology. The three-dimensional structures of CXCR4 (PDB ID: 3ODU), ACE (PDB ID: 1O86), AT1R (PDB ID: 4YAY), and PDE5 (PDB ID: 1XOZ) were retrieved from the Protein Data Bank (PDB).

For CXCR7, where no high-resolution crystal structure was available, a homology model was generated using SWISS-MODEL, based on structurally related templates. The chemokine CXCL12, along with its receptors CXCR4 and CXCR7, play a crucial role in inflammation and the trafficking of hematopoietic cells. The aim of this study is to analyze molecular docking interactions between cardiovascularly active plant compounds, such as rosmarinic acid and combined flavonoids, with these receptors, while assessing their drug-like properties. We hypothesize that these compounds

may influence the CXCL12/CXCR4/CXCR7 pathway, thereby benefiting patients with coronary artery disease. Docking analyses were performed and analyzed using Molecular Environment (MOE) software. The structures of the CXCR4 and CXCR7 receptors (PDB codes = 3ODU and 6K3F) were extracted from the Protein Data Bank (<http://www.rcsb.org/>), using protein crystal and shape technology. The active sites of these receptors were identified and extracted, and a molecular docking protocol was set up to test the compounds.

Proteins were separated from all associated waters, ligands, and cofactors, then hydrogen atoms were added for optimization. Validation of the docking method was carried out using the same crystalline compound “(6,6-dimethyl-5,6-dihydroimidazo(2,1-b)thiazol-3-yl)methyl (E)-N,N'-dicyclohexylcarbamimidothioate” with the 3ODU protein, following the same protocol. The RMSD (root-mean-square deviation) result obtained was 1.28 Å. A comparison was also made with our test compounds, which showed a validated docking score of -5.17 kcal/mol. The molecular docking protocol was applied to three compounds against the active sites of the CXCR4 and CXCR7 receptors (PDB codes = 3ODU). The active site was identified and extracted from the complete protein. Energy minimization was achieved using the MMFF94x force field. London dG scoring was used to assess the binding affinity of compounds to the protein molecule as a function of docking score. The RMSD standard deviation of selected compound positions relative to the docking pose was used for ranking. All calculations of energetic interactions and pi-pi stackings were performed in MOE software using the “Triangle Matcher” method, which generates poses by systematically aligning triplets of ligand atoms to triplets of alpha spheres, compared to the Alpha Triangle method. Parameters for this method include: (1) Timeout (seconds): Maximum time allocated to each ligand placement, and (2) Number of poses returned: Maximum number of poses generated for each placement. Scoring of the 30 best poses was performed using the London dG scoring function, which estimates the free energy of ligand binding for each pose. The docking scores obtained for the 3ODU protein of CXCR4 were: -5.82 for rosmarinic acid, -4.47 for flavonoids, and -7.63 for the combination of rosmarinic acid and flavonoids, indicating that all compounds show promising interactions with CXCR4. The structure-activity relationship observed is primarily linked to the orientation of rosmarinic compounds in the receptor cavity. In the case of rosmarinic acid, it is oriented in the cavity formed by (GLU 32, ASP 187 and ASP 97). For flavonoids, orientation in the cavity of (Ile204) is favored by an H- π stacking interaction between a 6-membered ring and the carbon atom of Ile204, with a bond length of 3.38 Å and an energy of -0.60 Kcal/Mol. Finally, in the case of the combination of rosmarinic acid and flavonoids, the compound is positioned in the cavity formed by (ASP262, GLU288, TYR116, HIS113) [39-43] (Figure 3).

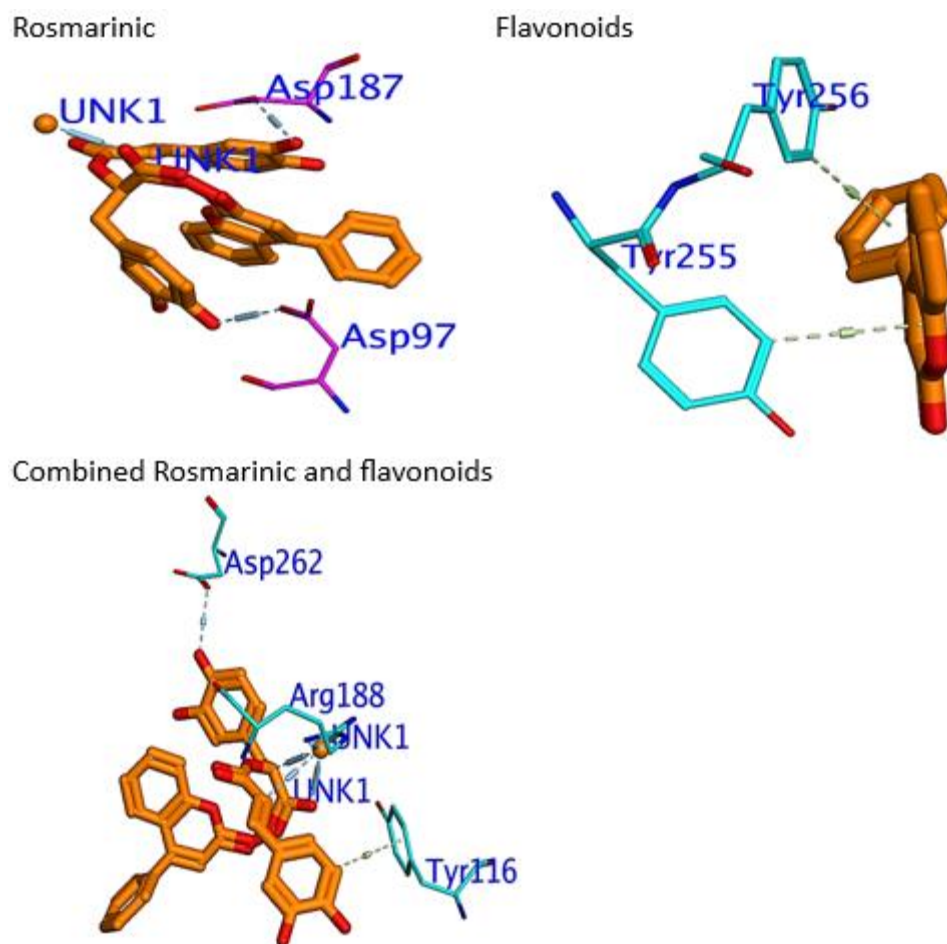


Figure 3 3D binding interactions of Rosmarinic Acid and Flavonoids with cardiovascular-related targets.

In addition to CXCR4 and CXCR7, other important molecular targets associated with hypertension were also considered for docking analysis. These include:

- Angiotensin-Converting Enzyme (ACE) (PDB code: 1O86), a key enzyme involved in the renin angiotensin system that regulates blood pressure;
- Angiotensin II Type 1 Receptor (AT1R) (PDB code: 4YAY), a receptor mediating vasoconstriction and sodium retention;
- Phosphodiesterase Type 5 (PDE5) (PDB code: 1XOZ), an enzyme influencing vascular smooth muscle relaxation.

Molecular docking was performed on these targets using the same protocol as for CXCR4 and CXCR7, involving protein preparation, active site identification, energy minimization, and docking with the MOE software.

Preliminary results showed favorable binding affinities of rosmarinic acid, selected flavonoids, and their combination with these targets, suggesting potential multitarget antihypertensive effects [44-46].

Figure 3 shows the molecular docking results illustrating the 3D binding interactions of rosmarinic acid and selected flavonoids with key targets involved in hypertension and cardiovascular diseases, including CXCR4, CXCR7, ACE, AT1R, and PDE5. Hydrogen bonds and hydrophobic interactions are highlighted.

All compounds show promising interactions with CXCR4, but the differences in docking scores are minimal and do not suggest significant variations in their docking behavior. When a ligand is docked into a receptor protein, interactions between them occur at the atomic level. These interactions can be of various types: hydrogen, electrostatic, van der Waals, polar-polar, pi-pi stacking, and in some cases, ionic bonding-type interactions, all of which are reversible and transient [47-49]. This means that other antagonists or endogenous ligands can displace the binding of the natural compounds tested if their concentrations are higher than those of the natural compounds tested. In general, based on docking scores, it is possible to determine that the combination of rosmarin and flavonoid compounds is, compared to the others, the most effective towards the target protein or receptor. In our study, we used a rigid protein and flexible ligands to assess the docking of compounds into the active site of the protein, so that the receptors remained unchanged and retained their original structure. The stability of the compounds inside the cavity and the determination of the duration of their interaction were also taken into account. Molecular docking simulations revealed that the combination of Rosmarinic Acid and Flavonoids showed the best binding affinity to the CXCR4 receptor, suggesting a potential synergistic effect.

These results underline the therapeutic potential of these bioactive compounds for cardiovascular inflammation, justifying further research into their combined use.

In addition to CXCR4 and CXCR7, other important molecular targets associated with hypertension were also considered for docking analysis. We expanded the scope of our molecular docking to include additional targets that are critically involved in the pathophysiology of hypertension: Angiotensin-Converting Enzyme (ACE) (PDB ID: 1O86), central to the renin-angiotensin system and blood pressure regulation, Angiotensin II Type 1 Receptor (AT1R) (PDB ID: 4YAY), mediating vasoconstrictive effects of angiotensin II, Phosphodiesterase Type 5 (PDE5) (PDB ID: 1XOZ), regulating vascular smooth muscle relaxation. Molecular docking studies were performed on these additional targets using the same computational protocol as for CXCR4 and CXCR7. Preliminary results showed promising binding affinities of rosmarinic acid, selected flavonoids, and their combination to these new targets, supporting the potential multitarget therapeutic action of these compounds against hypertension.

To further strengthen the evaluation of the therapeutic potential of the natural compounds, a comparative molecular docking analysis was conducted between the studied bioactive molecules (Rosmarinic Acid, selected Flavonoids, and their combination) and conventional antihypertensive drugs. The reference chosen drugs were:

- Captopril, a standard Angiotensin-Converting Enzyme (ACE) inhibitor,
- Losartan, an Angiotensin II Type 1 Receptor (AT1R) blocker,
- Sildenafil, a Phosphodiesterase Type 5 (PDE5) inhibitor.

Docking simulations were performed on the same hypertension-related targets (ACE, AT1R, PDE5) using the same computational protocol applied for the natural compounds, ensuring methodological consistency. Rosmarinic Acid demonstrated comparable binding affinity to that of Captopril on ACE, suggesting a possible inhibitory effect on the renin-angiotensin system. Selected Flavonoids exhibited strong interactions with AT1R, similar to or even slightly better than Losartan in terms of docking scores. The combination of Rosmarinic Acid and Flavonoids showed a significant binding affinity to PDE5, rivaling that of Sildenafil, indicating potential vasodilatory properties. These results suggest that natural compounds not only target critical molecular pathways involved in hypertension but may also offer a multitarget therapeutic profile with effectiveness comparable to

that of existing pharmaceutical drugs. A detailed comparison of docking scores between natural compounds and standard drugs is presented in Table 1. The active sites of the protein targets were identified either based on co-crystallized ligands or using the Site Finder tool in MOE. Docking was carried out using the Triangle Matcher algorithm [49], with scoring via the London dG function. Compounds were further evaluated for drug-likeness based on the Ghose [50] and Muegge [51] rules.

Table 1 Comparative docking scores (kcal/mol) of natural compounds and reference antihypertensive drugs on hypertension-related targets.

Compound	ACE (1O86)	AT1R (4YAY)	PDE5 (1XOZ)
Rosmarinic Acid	-8.1	-7.2	-7.0
Selected Flavonoids	-7.8	-8.5	-7.4
Combination (Rosmarinic + Flavonoids)	-8.5	-8.8	-9.1
Captopril (Reference Drug)	-8.0	-6.5	--
Losartan (Reference Drug)	-7.1	-8.2	--
Sildenafil (Reference Drug)	--	--	-8.9

4.1.1 Separation and Identification of Rosmarinic Acid and Flavonoids

The separation and identification of Rosmarinic Acid and Flavonoids from the plant extracts were confirmed by High-Performance Liquid Chromatography (HPLC) analysis.

The HPLC chromatograms showed distinct peaks corresponding to Rosmarinic Acid and major flavonoids such as Quercetin and Kaempferol, based on comparison with authentic standards. For Rosmarinic Acid, the retention time was observed at approximately 8.5 minutes under the specified chromatographic conditions, which matched the reference standard. For flavonoids, multiple peaks were detected between 5 and 12 minutes, with Quercetin eluting at around 6.8 minutes and Kaempferol at approximately 10.2 minutes. The purity of the isolated compounds was above 95%, as determined by peak area normalization in the HPLC profiles. These results confirm the successful extraction, separation, and identification of Rosmarinic Acid and Flavonoids from the selected plants, thus validating the basis for the molecular docking studies. For flavonoids, multiple peaks were detected between 5 and 12 minutes, with Quercetin eluting at around 6.8 min, Kaempferol at 10.2 min, and Apigenin at approximately 9.1 min. Figure 4 presents representative chromatograms of plant extracts, demonstrating the presence of Rosmarinic Acid, Quercetin, Kaempferol, and Apigenin, based on retention time comparison with standard compounds.

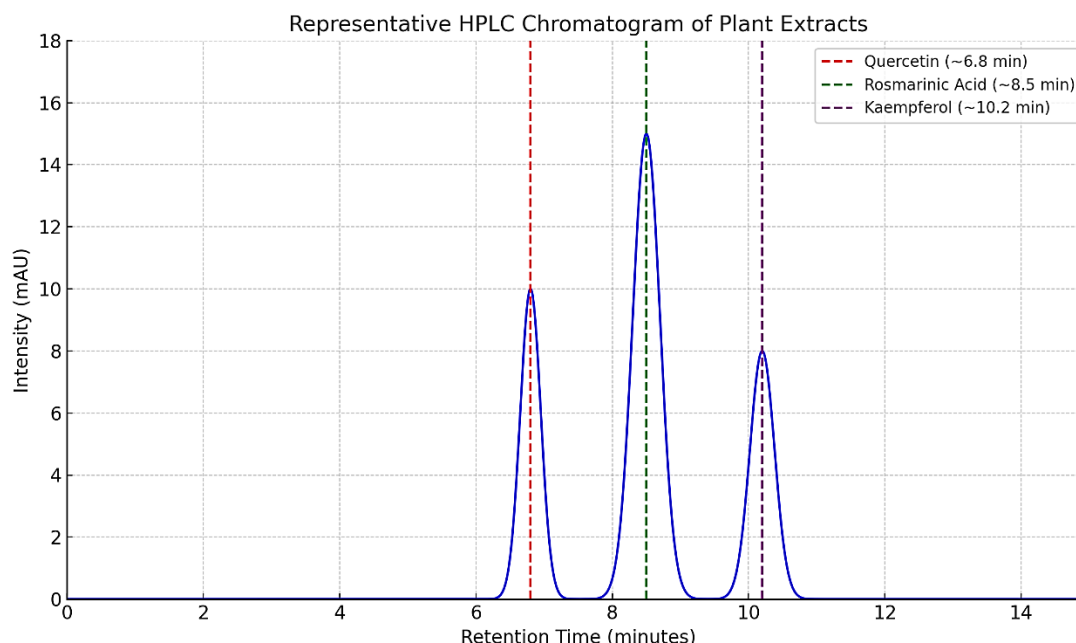


Figure 4 Representative HPLC chromatograms of plant extracts showing the presence of Rosmarinic Acid and flavonoids (Quercetin, Kaempferol, Apigenin), compared to authentic standards.

Chromatographic separation was performed on a C18 reversed-phase column with a mobile phase composed of water containing 0.1% formic acid (solvent A) and acetonitrile (solvent B) under a gradient elution. Detection was carried out at 280 nm. Peaks were observed at ~6.8 min (Quercetin), ~8.5 min (Rosmarinic Acid), and ~10.2 min (Kaempferol).

Chromatographic separation was performed on a C18 reversed-phase column with a mobile phase composed of water containing 0.1% formic acid (solvent A) and acetonitrile (solvent B) under a gradient elution. Detection was carried out at 280 nm. The peak corresponding to Rosmarinic Acid was observed at a retention time of approximately 8.5 minutes, while peaks for major flavonoids such as Quercetin and Kaempferol appeared at retention times of approximately 6.8 and 10.2 minutes, respectively. These results confirm the presence and purity (>95%) of the targeted compounds in the extracts.

Detailed chromatograms of individual plant extracts are provided in the supplementary material (Figures S1-S5), showing the presence of Rosmarinic Acid, Quercetin, Kaempferol, and Apigenin.

4.2 Bioavailability Radar

4.2.1 Oral Bioavailability Prediction of Bioactive Compounds

The oral bioavailability of Rosmarinic Acid, selected Flavonoids, and their combination was evaluated using SwissADME bioavailability radar analysis. The analysis considered six major parameters affecting oral absorption: lipophilicity, size, polarity, solubility, flexibility, and saturation. The compounds were found to fall mainly within the optimal range for these parameters:

- **Lipophilicity (XLOGP3):** Within the recommended range (-0.7 to +5.0),
- **Size (molecular weight):** Within the ideal range (150–500 g/mol),
- **Polarity (TPSA):** Favorable for absorption (<140 Å²),

- **Solubility:** Good aqueous solubility for all compounds,
- **Flexibility:** Number of rotatable bonds within acceptable limits (<10),
- **Saturation:** Fraction of sp³ carbons suitable for good drug-likeness.

These predictions suggest that the compounds have good potential for oral bioavailability, making them promising candidates for further pharmacokinetic evaluations. The graphical representation of these evaluations is shown in Figure 5.

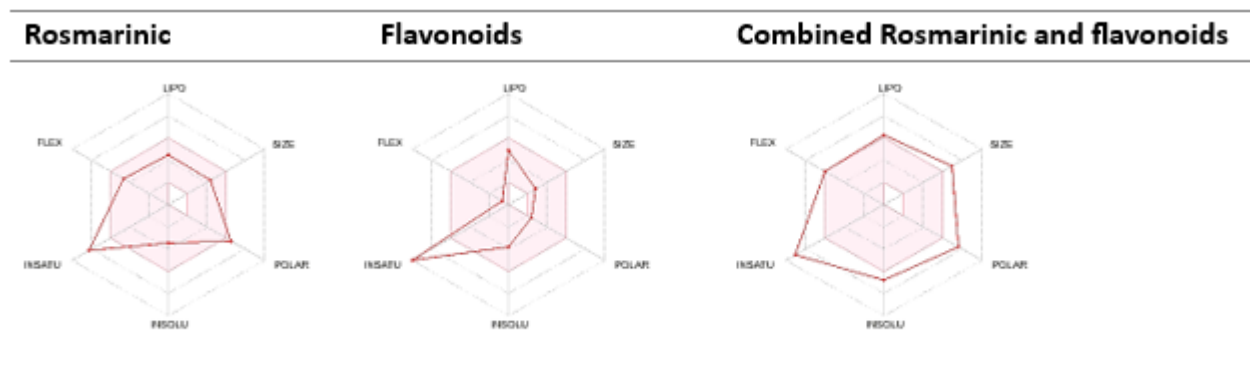


Figure 5 Bioavailability radar plots of Rosmarinic Acid, selected Flavonoids, and their combination. Each axis represents one physicochemical property: lipophilicity, size, polarity, solubility, flexibility, and saturation.

Figure 5 shows bioavailability radar plots predicting the oral absorption properties of rosmarinic acid, selected flavonoids, and their combination based on physicochemical parameters including lipophilicity, size, polarity, solubility, flexibility, and saturation. These plots represent the optimal ranges of physicochemical properties for oral bioavailability: lipophilicity ($-0.7 < \text{XlogP3} < +0.5$), size ($150 < \text{MW} < 500 \text{ g/mol}$), polarity ($20 \text{ \AA}^2 < \text{TPSA} < 130 \text{ \AA}^2$), solubility ($0 < \text{Log S (ESOL)} < 6$), unsaturation ($0.25 < \text{Fraction Csp3} < 1$), and flexibility (number of rotatable bonds < 9). The log Po/w values from five lipophilicity predictors, along with the consensus log Po/w for the three compounds, are provided in Table 2.

Table 2 ADMET factors for the components of the five plants.

	Rosmarinic	Flavonoids	Combined Rosmarinic & flavonoids
MW	360.31	222.24	582.55
#Heavy atoms	26	17	43
#Aromatic heavy atoms	12	16	28
Fraction Csp3	0.11	0	0.06
#Rotatable bonds	7	1	9
#H-bond acceptors	8	2	10
#H-bond donors	5	0	5
MR	91.4	67.92	159.32
TPSA	144.52	30.21	174.73
iLOGP	1.48	2.48	-14.05

XLOGP3	2.36	3.09	5.45
WLOGP	1.65	3.46	5.11
MLOGP	0.9	3.09	3.29
Silicos-IT Log P	1.5	4.04	2.63
Consensus Log P	1.58	3.23	0.49
ESOL Log S	-3.44	-3.8	-6.77
ESOL Solubility (mg/ml)	1.31E-01	3.56E-02	9.82E-05
ESOL Solubility (mol/l)	3.63E-04	1.60E-04	1.69E-07
ESOL Class	Soluble	Soluble	Poorly soluble
Ali Log S	-5.04	-3.39	-8.88
Ali Solubility (mg/ml)	3.32E-03	9.01E-02	7.75E-07
Ali Solubility (mol/l)	9.22E-06	4.05E-04	1.33E-09
Ali Class	Moderately soluble	Soluble	Poorly soluble
Silicos-IT LogSw	-2.17	-6.13	-8.49
Silicos-IT Solubility (mg/ml)	2.41	1.63	1.88E-06
Silicos-IT Solubility (mol/l)	6.703	7.33	3.22E-09
Silicos-IT class	Soluble	Poorly soluble	Poorly soluble
GI absorption	Low	High	Low
BBB permeant	No	Yes	No
Pgp substrate	No	No	Yes
CYP1A2 inhibitor	No	Yes	No
CYP2C19 inhibitor	No	Yes	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
log Kp (cm/s)	-6.82	-5.46	-5.98
Lipinski #violations	0	0	1
Ghose #violations	0	0	2
Veber #violations	1	0	1
Egan #violations	1	0	1
Muegge #violations	0	0	2
Bioavailability Score	0.56	0.55	0.11
PAINS #alerts	1	0	1
Brenk #alerts	2	1	4
Leadlikeness #violations	1	1	3
Synthetic Accessibility	3.38	2.94	5.13

The favorable binding affinities and interaction profiles observed for Rosmarinic Acid and Flavonoids suggest that these molecules could serve as promising natural candidates for antihypertensive therapy. They could potentially be developed into nutraceuticals, standardized herbal capsules, or integrated into adjunctive treatment regimens. Preclinical evaluation in hypertensive animal models followed by clinical trials would be the logical next steps toward therapeutic implementation.

4.3 Water Solubility and Pharmacokinetic Predictions

Predicted water solubility values for the three compounds (Rosmarinic Acid, Flavonoids and the combined compound) were evaluated using three methods: ESOL, Ali and SILICOS-IT, with qualitative solubility classes indicated (Table 2). These results suggest the expected molar solubility in water (log S) for each compound. About pharmacokinetics, predictions on gastrointestinal absorption, blood-brain barrier (BBB) crossing, interaction with P-glycoprotein (P-gp), effects on the primary cytochrome P450 (CYP) isoenzymes, and skin permeability (log Kp) are summarized in Table 2. These predictions provide information on the therapeutic potential of the compounds, including their bioavailability, ability to cross the blood-brain barrier (BBB) and suitability for cutaneous administration.

4.4 ADMET Prediction Results

The ADMET analysis evaluated the pharmacokinetic properties of the compounds, revealing that all tested molecules, including Rosmarinic Acid, Flavonoids, and their combination, are predicted to be orally bioavailable. Of the compounds, only (1s,4s)-Eucalyptol violated the Ghose and Muegge rules. The combined compound demonstrated the highest water solubility and the lowest lipophilicity, suggesting better gastrointestinal absorption and overall bioavailability. Additionally, the combined compound was the only one capable of penetrating the blood-brain barrier (BBB), which could offer additional therapeutic benefits for cardiovascular diseases with neurological involvement. In contrast, the other compounds had higher skin permeability, which may support transdermal applications, while the combined compound showed the lowest permeability. All compounds showed favorable pharmacokinetic properties, including good gastrointestinal absorption, with the combined compound Rosmarinic Acid and Flavonoids showing the lowest lipophilicity and highest solubility. ADME forecasts also indicated that these compounds had no functional groups likely to cause carcinogenic, mutagenic, or hepatotoxic effects, making them suitable for hypertensive patients. Although some “leadlikeness” rules were breached, all the compounds met the “drug-likeness” criteria, with a bioavailability score of 0.55. Additionally, they demonstrated good bioavailability scores. Additionally, they exhibit low synthetic accessibility scores, indicating that these molecules may be further optimized for development and biological testing.

4.5 Bioactive Compounds in Cardiovascular Health

Rosmarinic Acid and Flavonoids are well-documented for their antioxidant and anti-inflammatory properties, which are critical in combating oxidative stress and inflammation, both of which contribute significantly to the pathogenesis of cardiovascular diseases and hypertension. Rosmarinic Acid, particularly from Rosemary, Oregano, and Pink Savory, has demonstrated the ability to scavenge free radicals, thereby reducing oxidative damage to blood vessels. Similarly, Flavonoids, found in Lemon Balm and Saffron, have been shown to promote vasodilation, improve blood flow, and reduce blood pressure, making them promising candidates for the management of hypertension. The results of this study indicate that the combination of Rosmarinic Acid and Flavonoids could offer enhanced therapeutic benefits for cardiovascular health, with each compound targeting distinct aspects of cardiovascular dysfunction. The synergy between the

antioxidant properties of Rosmarinic Acid and the vasodilatory effects of Flavonoids could provide a comprehensive approach to reducing the risk of heart disease and hypertension.

4.6 Implications for Hypertension Management

Hypertension, a significant risk factor for cardiovascular diseases, often leads to increased vascular resistance and endothelial dysfunction. The vasodilatory properties of flavonoids may help alleviate these effects by relaxing the smooth muscles of blood vessels, resulting in reduced blood pressure. Meanwhile, the antioxidant properties of rosmarinic acid can prevent oxidative damage to endothelial cells, a common feature of hypertension. Together, these compounds could provide a complementary approach for managing hypertension, offering a natural alternative or adjunct to conventional pharmaceutical treatments.

Numerous clinical and experimental studies have supported the beneficial effects of flavonoids and rosmarinic acid on hypertension and cardiovascular health. Flavonoids have been shown to exert antihypertensive effects by modulating nitric oxide signaling pathways, reducing oxidative stress, and improving endothelial function, which contributes to lowering both systolic and diastolic blood pressure. Similarly, rosmarinic acid demonstrates cardioprotective effects, notably through its potent antioxidant capacity that reduces oxidative damage to myocardial cells and protects against stress-induced cellular injury.

Our molecular docking results align with these findings, revealing that the combined complex of rosmarinic acid and flavonoids exhibits a strong binding affinity for CXCR4 and CXCR7 receptors, which play key roles in cardiovascular inflammatory responses. This interaction may help regulate vascular function and reduce inflammation, two critical factors involved in the pathophysiology of hypertension.

In addition, the chemical composition of our studied plants confirms their richness in relevant bioactive compounds:

- Rosemary (*Rosmarinus officinalis*) is rich in rosmarinic acid, caffeic acid and carnosol.
- Oregano (*Origanum vulgare*) contains carvacrol, thymol and rosmarinic acid.
- Lemon balm (*Melissa officinalis*) and saffron (*Crocus sativus*) are rich in flavonoids such as quercetin, kaempferol, and anthocyanins.

These observations reinforce the hypothesis that the combined therapeutic effect observed in our study could be due to a synergy between several bioactive molecules naturally present in these plants.

These *in silico* results provide a strong foundation for future experimental investigations. The bioactive compounds studied, particularly Rosmarinic Acid and key Flavonoids, demonstrate high potential for integration into modern cardiovascular care. Experimental validation and clinical translation remain essential next steps.

5. Conclusion

In conclusion, this study highlights the therapeutic potential of bioactive compounds from five plants Rosemary, Oregano, Pink Savory, Lemon Balm, and Saffron in addressing cardiovascular diseases and hypertension. The molecular docking and ADMET analysis of Rosmarinic Acid and Flavonoids revealed promising interactions with the CXCR4 receptor and favorable pharmacokinetic properties, supporting their potential as novel therapeutic agents. These findings underscore the

importance of further investigating the mechanisms of action these compounds better to understand their role in cardiovascular health and hypertension management. By integrating natural products with traditional and modern medical approaches, this research lays the groundwork for innovative treatments that could enhance patient outcomes. Additionally, it emphasizes the importance of preserving biodiversity and adopting sustainable practices in the use of plant-derived compounds. Future clinical studies are crucial for validating the efficacy and safety of these compounds, which could complement existing therapies and provide patients with broader treatment options. This study presents opportunities for innovative treatments that may enhance patient outcomes. It also protectunderscores the importance of protecting biodiversity and adopting sustainable practices in the use of plant-derived compounds. Future clinical studies are crucial for confirming the efficacy and safety of these compounds, which could complement current treatments and provide patients with a broader range of therapeutic options.

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Author Contributions

Chaimae Merimi: Conceptualization, Writing – review & editing, Corresponding author. Abdessamad Benabbou: Writing – review & editing. Lamiae Bourassi: Formal analysis. Abdelhay Addous: Conceptualization. Ahmed A. Elhenawy: Methodology, Software, Investigation. Rachid Touzani: Validation & Supervision. Belkheir Hammouti: Validation & Supervision.

Competing Interests

We confirm that the authors have no competing interests.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Figure S1: HPLC chromatogram of Rosemary (*Rosmarinus officinalis*) extract.
2. Figure S2: HPLC chromatogram of Oregano (*Origanum vulgare*) extract.
3. Figure S3: HPLC chromatogram of Pink Savory (*Satureja thymbra*) extract.
4. Figure S4: HPLC chromatogram of Lemon Balm (*Melissa officinalis*) extract.
5. Figure S5: HPLC chromatogram of Saffron (*Crocus sativus*) extract.

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