

T.R.
GEBZE TECHNICAL UNIVERSITY
GRADUATE SCHOOL

**DISCOVERY OF PLANT-BASED PHENOLIC COMPOUNDS
FOR THE TREATMENT OF PSORIASIS AND ATOPIC
DERMATITIS**

SİNEM NUR YAYLA

A THESIS OF MASTER OF SCIENCE
DEPARTMENT OF BIOTECHNOLOGY

ADVISOR: ASSOC. PROF. MEHMET OZBIL

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GEBZE TEKNİK ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ**

**SEDEF HASTALIĞI VE ATOPİK DERMATİT İLE
MÜCADELE İÇİN BİTKİ BAZLI FENOLİK
BİLEŞİKLERİN KEŞFİ**

SİNEM NUR YAYLA

**YÜKSEK LİSANS TEZİ
BİYOTEKNOLOJİ ANABİLİM DALI**

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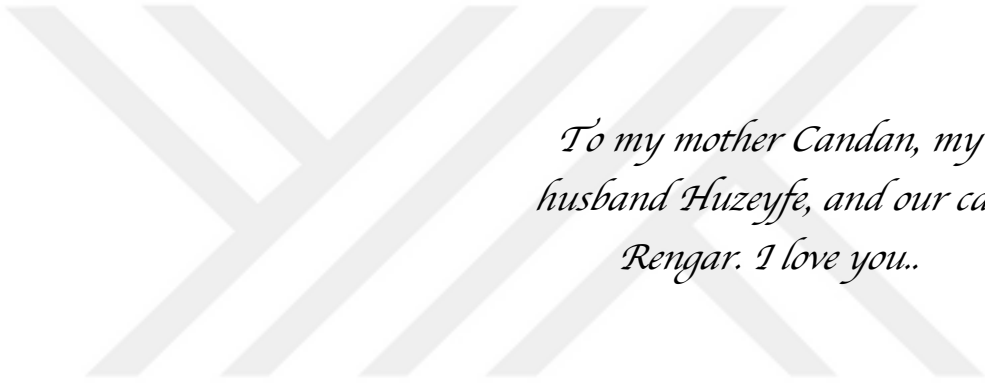
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*To my mother Candan, my
husband Huzeyfe, and our cat
Rengar. I love you..*

ABSTRACT

Psoriasis and atopic dermatitis (AD) are chronic inflammatory skin diseases that significantly affect quality of life and are based on complex immune system dysfunctions. Current treatment approaches are often limited to suppressing symptoms, and long-term use can lead to serious side effects and the development of resistance to treatment. Therefore, there is an increasing need for safer, more effective, and sustainable alternative treatment options. In recent years, plant-based natural products such as phenolic compounds have emerged as potential biological agents in the treatment of many chronic inflammatory diseases due to their anti-inflammatory, antioxidant, and immunomodulatory effects.

The study identified psoriasis and atopic dermatitis target proteins through a literature review. The STRING database allowed the construction of a PPI network that revealed the relationships between these proteins. AlphaFold generated target protein models for CABS-flex to evaluate their alternative conformations. In this study, phenolic compounds with high therapeutic potential, including those found in *Taraxacum officinale* (dandelion), *Silybum marianum* (milk thistle), and *Brassica nigra* (black mustard), were obtained from the PubChem server. Molecular docking analysis was performed to evaluate the interactions between the resulting phenolic compounds and target proteins. After docking, the resulting protein-ligand poses were ranked according to their highest binding affinity and then subjected to GROMACS-based molecular dynamics (MD) simulations to investigate their structural stability and dynamic behavior. To understand the dynamics of the protein-ligand complexes throughout the simulation, parameters such as root mean square deviation (RMSD), relative density (Rg), relative density (SASA), and number of hydrogen bonds were analyzed. In addition to these analyses, MM/GBSA analysis was performed to visualize the change in the binding energy of the protein-ligand complexes throughout the simulation, and an average binding energy was obtained. This study demonstrated that phenolic compounds derived from three different plants exhibited strong binding properties and structural stability when interacting with target proteins involved in psoriasis and atopic dermatitis disease pathways. These compounds could be potential therapeutic agents for the future, as future clinical studies support their potential applications.

Keywords: Psoriasis, Atopic Dermatitis, Phenolic Compounds, Plant-Based Treatment, Molecular Docking, Molecular Dynamics Simulation

ÖZET

Sedef hastalığı ve atopik dermatit (AD), bağışıklık sistemindeki karmaşık işleyiş bozukluklarına dayanan, kronik, tekrarlayıcı ve yaşam kalitesini önemli ölçüde etkileyen enflamatuvar deri hastalıklarıdır. Mevcut tedavi yaklaşımları, çoğu zaman semptomları baskılamakla sınırlı kalmakta, uzun vadeli kullanımda ise ciddi yan etkiler ve tedaviye karşı direnç gelişimi gibi sorunlar ortaya çıkabilmektedir. Bu nedenle, daha güvenli, etkili ve sürdürülebilir alternatif tedavi seçeneklerine duyulan ihtiyaç giderek artmaktadır. Son yıllarda, fenolik bileşikler gibi bitki bazlı doğal ürünler, anti-enflamatuvar, antioksidan ve immünmodülatör etkileri sayesinde birçok kronik inflamatuvar hastalığın tedavisinde potansiyel biyolojik ajanlar olarak öne çıkmaktadır.

Bu çalışmada, literatür taraması yoluyla sedef hastalığı ve atopik dermatit ile ilişkili ortak hedef proteinler belirlenmiş, bu proteinler arasındaki etkileşimleri ortaya koymak amacıyla STRING veritabanı kullanılarak protein-protein etkileşim (PPI) ağı oluşturulmuştur. Elde edilen hedef proteinler AlphaFold aracılığıyla modellenmiş, ardından proteinlerin alternatif konformasyonları CABS-flex aracıyla analiz edilmiştir. Terapötik potansiyelleri yüksek olduğu bilinen *Taraxacum officinale* (karahindiba), *Silybum marianum* (devediken) ve *Brassica nigra* (kara hardal) bitkilerine ait fenolik bileşikler, PubChem veritabanından elde edilerek çalışmaya dahil edilmiştir. Seçilen fenolik bileşikler ile hedef proteinler arasındaki bağlanma afiniteleri, Smina yazılımı kullanılarak gerçekleştirilen moleküler yerleştirme (docking) simülasyonları ile değerlendirilmiştir. En güçlü bağlanma skorlarına sahip protein-ligand kompleksleri, yapısal stabiliteyi ve dinamik davranışlarını incelemek amacıyla GROMACS tabanlı moleküler dinamik (MD) simülasyonlarına tabi tutulmuştur.

Simülasyon sonuçları, RMSD, Rg, SASA ve hidrojen bağları gibi parametreler üzerinden analiz edilmiştir. Ayrıca, protein-ligand bağlanma enerjilerinin daha hassas bir şekilde hesaplanabilmesi için MM/GBSA serbest enerji hesaplamaları gerçekleştirilmiştir. Elde edilen bulgular, özellikle belirli fenolik bileşiklerin, sedef hastalığı ve atopik dermatit tedavisinde hedef proteinlerle yüksek bağlanma afinitesi ve yapısal kararlılık gösterdiğini ortaya koymuştur. Bu veriler, bu bileşiklerin gelecekte biyolojik doğrulama ve klinik çalışmalarla desteklenebilecek potansiyel terapötik ajanlar olabileceğini göstermektedir.

Anahtar Kelimeler: Sedef Hastalığı, Atopik Dermatit, Fenolik Bileşikler, Bitki Bazlı Tedavi, Moleküler Yerleştirme, Moleküler Dinamik Simülasyonu

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TABLE OF CONTENTS

	<u>Page</u>
ABSTRACT	vi
ÖZET	vii
ACKNOWLEDGEMENTS	viii
TABLE OF CONTENTS	ix
LIST OF SYMBOLS AND ABBREVIATIONS	xi
LIST OF FIGURES	xiii
LIST OF TABLES	xiv
 1.INTRODUCTION	 1
1.1 Background Information Psoriasis and Atopic Dermatitis	1
1.1.1 Clinical and Social Economic Burden	1
1.2 Immunopathogenesis of Psoriasis and Atopic Dermatitis	2
1.3 Limitations of Current Treatment Strategies.	5
1.3.1 Systemic and Biologic Therapies	5
1.3.2. Patient Challenges and Interest in Phytotherapy	7
1.4. Traditional Roots and Scientific Foundations of Phytotherapy	8
1.4.1. Phytochemical Classes and Mechanisms of Action.	10
1.4.2. Global Trends and Scientific Validation of Phytotherapy	10
1.5. Therapeutic Potential and Mechanisms of Selected Plants	12
1.5.1. Milk Thistle (<i>Silybum marianum</i>)	12
1.5.2. Black Mustard (<i>Brassica nigra</i>)	15
1.5.3. Dandelion (<i>Taraxacum officinale</i>)	17
1.6. Comparative Evaluation of Selected Medicinal Plants	19
1.7. Sustainability and Environmental Benefits of Phytotherapy	21
1.7.1. Green Chemistry in Herbal Medicine Production	23
1.8. Integration of Biotechnology and In Silico Tools in Phytotherapy Research	24
2. AIM OF THE STUDY	26
3. METHOD	27
3.1. Literature Review and Data Collection	27
3.2. Protein-Protein Interaction (PPI) Network Construction and Analysis	27
3.3. Prediction of Three Dimensional Protein Structures and Optimization	28
3.4. Preparation of Ligand Structures and Optimization	29
3.5. Molecular Docking Simulations	29
3.6 Molecular Dynamics (MD) Simulations	30
3.6.1 Analysis of MD Simulations	31
3.6.2 Binding Free Energy Calculations	33
4. RESULTS	35

4.1. Literature Review and Data Collection	35
4.2. Protein–Protein Interaction (PPI) Network Analysis	37
4.3. Generation of Alternative Protein Structures (CABS-flex)	40
4.4. Molecular Docking Simulations Analysis	41
4.5 Molecular Dynamics Simulations Analysis	44
4.5.1 RMSD Analysis	44
4.5.2. Solvent Accessible Surface Area (SASA) Analysis	46
4.5.3. Radius of Gyration (Rg) Analysis	46
4.5.4. Hydrogen Bond (H-Bond) Analysis	47
4.5.5. Binding Free Energy (ΔG) Analysis	48
5. DISCUSSION	51
6. CONCLUSION	55
REFERENCES	57
BIOGRAPHY	64
PUBLICATIONS AND PRESENTATIONS FROM THE THESIS.	65
APPENDICES	CD

LIST OF SYMBOLS AND ABBREVIATIONS

AD	: Atopic Dermatitis
ADMET	: Absorption, Distribution, Metabolism, Excretion, and Toxicity
AI	: Artificial Intelligence
AMBER94	: Assisted Model Building with Energy Refinement 1994
COX-2	: Cyclooxygenase-2
dA	: Surface Element
Δ	: Change
Δ EMM	: Molecular Mechanics Energy
Δ G _{bind}	: Binding Free Energy
Δ G _{solvation}	: Solvation Free Energy
DNA	: Deoxyribonucleic Acid
EMA	: European Medicines Agency
EM	: Energy Minimization
ERK	: Extracellular signal-Regulated Kinase
FDA	: Food and Drug Administration
GB	: Generalized Born
GO	: Gene Ontology
GPx	: Glutathione Peroxidase
IFN- γ	: Interferon gamma
iNOS	: Inducible Nitric Oxide Synthase
JAK	: Janus Kinase
JNK	: c-Jun N-terminal Kinase
LC-MS/MS	: Liquid Chromatography – Tandem Mass Spectrometry
LINCS	: Linear Constraint Solver
LPS	: Lipopolysaccharide
MAPK	: Mitogen-Activated Protein Kinase
m _i	: Mass of atom i
MM/GBSA	: Molecular Mechanics / Generalized Born Surface Area
MMFF94x	: Merck Molecular Force Field 1994 extended
MMPBSA	: Molecular Mechanics Poisson–Boltzmann Surface Area
MOE	: Molecular Operating Environment
MOL	: Molecule File
MSA	: Multiple Sequence Alignment
N	: Total Number of Atoms
NF- κ B	: Nuclear Factor “kappa B”
NMR	: Nuclear Magnetic Resonance
NPT	: Constant Number of Particles, Pressure, and Temperature
NVT	: Constant Number of Particles, Volume, and Temperature
PASI	: Psoriasis Area and Severity Index
PB	: Poisson–Boltzmann
PBC	: Periodic Boundary Conditions
PDB	: Protein Data Bank
p(r)	: Indicator Function
PB	: Poisson–Boltzmann
PPI	: Protein-Protein Interaction
QSAR	: Quantitative Structure–Activity Relationship

rcm	: Center-of-Mass Position of the Structure
ri	: i Position
ri(0)	: Initial Reference Position
ri(t)	: Coordinates of Atom i
RNA-seq	: RNA Sequencing
Rg	: Radius of Gyration
ROS	: Reactive Oxygen Species
RMSD	: Root Mean Square Deviation
SASA	: Solvent Accessible Surface Area
SDF	: Structure Data File
SDG 3	: Good Health and Well-Being
SDG 12	: Responsible Consumption and Production
SDG 13	: Climate Action
SDG 14	: Life Below Water
SDGs	: United Nations Sustainable Development Goals
SOD	: Superoxide Dismutase
SPC	: Simple Point Charge
SSRIs	: Selective Serotonin Reuptake Inhibitors
STAT	: Signal Transducer and Activator of Transcription
STRING	: Search Tool for the Retrieval of Interacting Genes/Proteins
t	: Simulation Time
TΔS	: Temperature × Entropy Change
TCM	: Traditional Chinese Medicine
Th2	: Type 2 Helper T Cell
TNF-α	: Tumor Necrosis Factor-Alpha
TYK2	: Tyrosine Kinase 2
UV	: Ultraviolet
UVB	: Ultraviolet B
WHO	: World Health Organization

LIST OF FIGURES

	<u>Page</u>
Figure 1.1: Psoriasis signaling pathway	3
Figure 1.2: Atopic dermatitis pathway	4
Figure 1.3: Structural representation of IL-17A	4
Figure 1.4: Milk thistle with chemical structures	13
Figure 1.5: Black mustard with chemical structures	15
Figure 1.6: Dandelion with chemical structures	18
Figure 1.7: Alignment of the Study with Selected Sustainable Development Goals	23
Figure 4.1: Protein–protein interaction network of literature-validated proteins	39
Figure 4.2: Extended interaction network comprising both primary and STRING enriched secondary proteins	40
Figure 4.3: Ten conformations of the IL17A protein were generated by CABS-flex	41
Figure 4.4: Bubble plot representation of frequently interacting ligands with target proteins.	42
Figure 4.5: The recurrence frequencies of ligands across the final 120 complexes	44
Figure 5.1: Chemical structures of flavonoids	54

LIST OF TABLES

Table 4.1: Shared Primary Proteins Identified in Both Psoriasis and Atopic Dermatitis Based on Literature	<u>Page</u> 36
Table 4.2: Primary Proteins Identified in Atopic Dermatitis and Psoriasis Pathways Based on Literature Review	37



1. INTRODUCTION

1.1. Information Psoriasis and Atopic Dermatitis

Chronic inflammatory skin diseases pose a significant public health problem worldwide due to their long-term symptoms, psychosocial effects, and treatment challenges. Among this group, the two most common diseases, psoriasis and atopic dermatitis (AD), affect hundreds of millions of people worldwide, characterized by persistent skin inflammation, severe itching, and a significant decline in quality of life (Laughter et al., 2021; Parisi et al., 2013). Both diseases are associated with immune system dysregulation and exhibit similar clinical features in terms of recurrent flare-ups and psychological burden. The traditional medical categorization of psoriasis as an autoimmune disease and atopic dermatitis as an allergic disorder has faced recent scientific evidence demonstrating similar immunological pathways and disease associations between the two conditions (Lowe et al., 2014; Brunner et al., 2017).

Psoriasis usually presents itself through sharply defined erythematous plaques which exhibit silver scaling that typically appear on the body extensor regions and scalp along with the trunk area. AD presents with persistent eczematous lesions and severe itching that causes skin thickening primarily affecting flexural skin areas in adults and facial and extensor surfaces in children (Langan et al., 2020). Although clinical symptoms differ among the conditions, they display similar histological patterns, which include epidermal hyperplasia together with impaired skin barrier function and inflammatory cell infiltration (Tsoi et al., 2012).

The stability and conformational dynamics of the protein–ligand complexes were evaluated through several trajectory analyses conducted using built-in GROMACS utilities.

1.1.1. Clinical and Socioeconomic Burden

The worldwide impact of psoriasis and AD on people extends beyond their physical health consequences into economic and psychological aspects. The global prevalence of psoriasis stands at 2–3% while AD affects 20% of children and 10% of adults within

industrialized nations according to Egeberg et al. (2017). The conditions lead to serious emotional difficulties which result in depression as well as anxiety alongside social withdrawal in affected individuals. Research evidence demonstrates that people with severe skin disease experience life quality at a comparable level to diabetes or cardiovascular disease patients (Kimball et al., 2005; Drucker, 2017).

These diseases cause substantial economic burdens because they require repeated doctor visits, hospitalizations, prescription medication costs and patient care expenses and lost productivity. Psoriasis generates more than \$100 billion in annual direct and indirect costs throughout the United States according to research by Brezinski et al. (2015). The economic impact along with the emotional consequences drive an urgent need for better sustainable therapeutic solutions.

1.2. Immunopathogenesis of Psoriasis and Atopic Dermatitis

The literature review shows that psoriasis and atopic dermatitis (AD) start with different cytokine “triggers” before they merge into identical intracellular circuitry (**Appendix Table A-1 Figures 1.1 and Figure 1.2**). The dendritic cells in psoriasis produce IL-12 and IL-23 that cause T cells to differentiate into Th1/Th17 cells which produce elevated levels of IL-17, IL-23 and TNF- α . The initial Th2 response in acute AD is driven by OX40L-bearing dendritic cells that produce IL-4, IL-5 and IL-13. The immune profile in chronic AD shifts over time to include Th1, Th17 and Th22 cells that release IL-17A and IL-22 cytokines that are characteristically associated with psoriasis (**Dainichi et al., 2018; Guttman-Yassky et al., 2011**). Notably, IL-17A plays a pivotal role in the pathogenesis of both diseases by binding to its receptor complex on keratinocytes, thereby triggering downstream signaling cascades that result in keratinocyte hyperproliferation and pro-inflammatory cytokine release. The structural interface between IL-17A and its receptor, as visualized in Figure 1.3, represents a critical pharmacological target in the development of anti-inflammatory therapies. These cytokines converge on shared intracellular pathways by activating Janus kinases (JAK1, JAK2, JAK3, TYK2), which phosphorylate transcription factors such as STAT3 and STAT4 in keratinocytes. Once phosphorylated, STAT dimers translocate to the nucleus to activate inflammatory genes including S100A8/A9, CXCL1/8, and IL-23A. This inflammatory loop is further amplified by TNF- α and

pattern-recognition receptors via the NF- κ B pathway. The shared JAK–STAT–NF- κ B signaling backbone of both diseases provides a rationale for using TYK2 inhibitors, pan-JAK inhibitors, and PDE4 inhibitors in their treatment. For the same mechanistic reasons, multi-target phytochemicals—such as silibinin, chlorogenic acid, and sinapic acid—are promising candidates, as they may simultaneously modulate multiple signaling cascades, supporting the development of a unified phytotherapeutic strategy for two distinct clinical entities with overlapping molecular signatures.

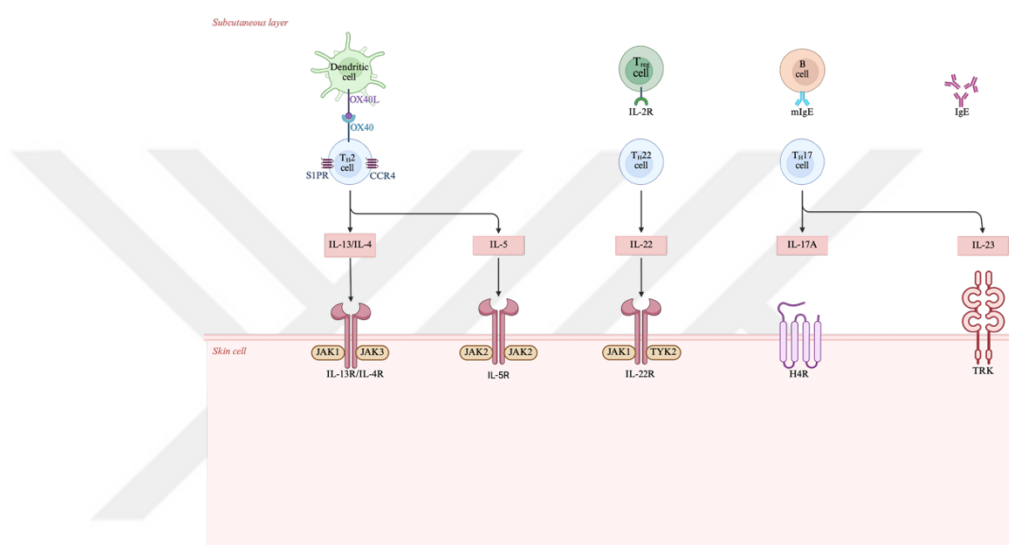


Figure 1.1. The figure shows how interleukin activates TYK2–JAK/STAT signaling pathways which maintain atopic dermatitis. The binding of IL-12, IL-23, IL-22 or IL-6 to their receptors activates TYK2/JAK1-2 kinases which results in STAT3 or STAT4 phosphorylation and subsequent dimerization and nuclear translocation. The transcription of IFNG and IL17A/F leads to the Th1/Th17 cytokine loop a keratinocyte hyperproliferation which defines psoriatic skin. Created with BioRender.com. Adapted from biorender template.

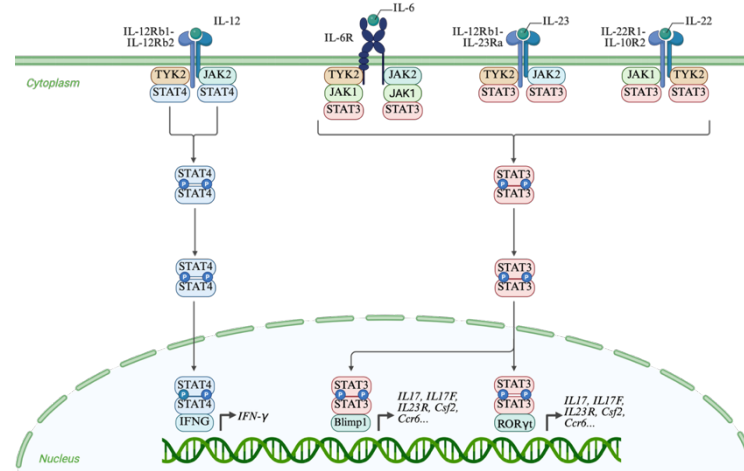


Figure 1.2. The figure shows how the adaptive immune system uses cytokine signaling to fight psoriasis. The OX40L signal from dendritic cells activates Th2 cells to produce IL-4, IL-13 and IL-5 which activate JAK1/3 or JAK2 in keratinocytes; IL-22 from Th22 cells activates JAK1–TYK2 while IL-17A from Th17 cells enhances inflammation through an IL-23 feedback loop. Created with BioRender.com. Adapted from **Guo et al., *Signal Transduct Target Ther*, 2023 (DOI: 10.1038/s41392-023-01655-6)**

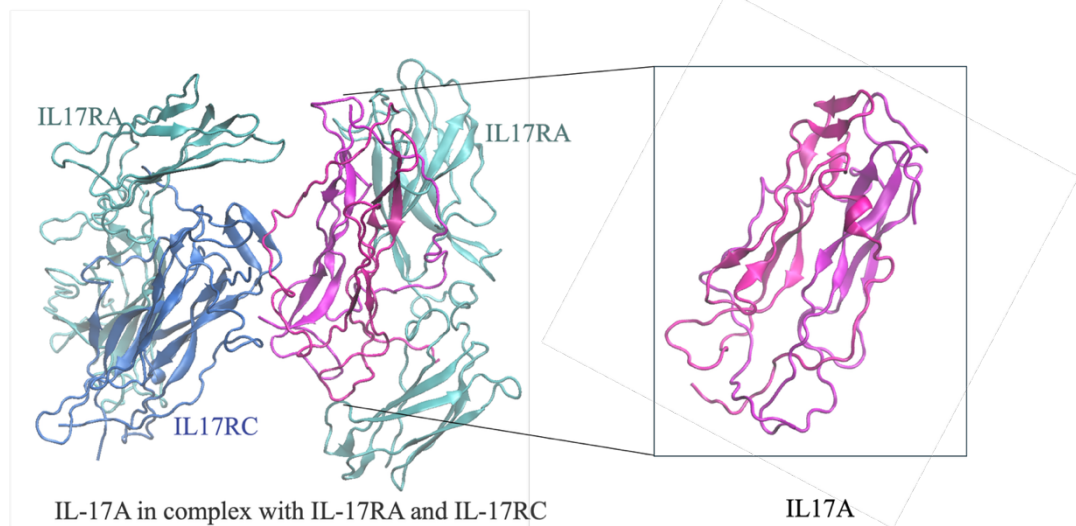


Figure 1.3. It shows the structural representation of IL-17A cytokine (magenta) in complex with its receptors IL-17RA (cyan) and IL-17RC (blue). The right panel shows the IL-17A homodimer structure extracted from the receptor complex, which shows its characteristic β-sheet-rich topology.

1.3. Limitations of Current Treatment Strategies

Modern dermatology has achieved various progress, but scientists have not established a definitive treatment for these diseases. Symptomatic relief with the existing treatments is insufficient because these drugs show weak long-term effectiveness. Moreover, they cause side effects, and they are not cost-beneficial (**Drucker et al., 2017; Kimball et al., 2005**). Researchers now focus on developing novel therapeutic methods because current treatment options lack sustainability and affordability according to modern healthcare principles (**Ekor, 2014**). The assessment of current treatment limitations creates a justification for expanding interest in phytotherapy along with integrative medical approaches (**Pan et al., 2014**).

The initial treatment approach for psoriasis and AD starts with topical corticosteroids. These agents suppress inflammation through inhibition of phospholipase A2, which leads to decreased eicosanoid generation in the downstream pathways. The extended application of these medications results in multiple severe side effects including skin atrophy, striae and telangiectasia, and tachyphylaxis (**Ference & Last, 2009**). Medical experts do not recommend the long-term use of topical corticosteroids, especially in sensitive areas such as the face and genital regions. The main reason for this is that unwanted side effects associated with the medication are more likely to develop quickly in these areas. The three most reported side effects are skin atrophy (thinning and a thin appearance of the skin), telangiectasia (the appearance of superficial capillaries), and perioral dermatitis (inflamed rashes that appear mainly around the mouth) (**Coondoo et al., 2014**). The introduction of topical calcineurin inhibitors including tacrolimus and pimecrolimus occurred to reduce existing treatment disadvantages. These medications block calcineurin to prevent T-cell activation as well as cytokine production. The therapeutic effect of these medications on mild-to-moderate AD remains limited because their use has been restricted due to unproven cancer risks during prolonged treatment (**Cury Martins et al., 2015**).

1.3.1. Systemic and Biologic Therapies

Systemic therapy refers to the use of pharmacologic agents that circulate throughout the body rather than acting only on the skin surface to modulate the immune and inflammatory pathways driving psoriasis and atopic dermatitis (AD). Topical

corticosteroids or calcineurin inhibitors function only in the specific area of application but systemic drugs distribute through the bloodstream to suppress immune responses in both skin and other body parts. These drugs help manage skin diseases of moderate to severe intensity more effectively. The immune system receives general suppression from methotrexate and cyclosporine and azathioprine but biological agents like TNF- α and IL-17 and IL-4/13-targeted drugs specifically target immune pathways to produce a more targeted effect **(Armstrong & Read, 2020; Menter et al., 2019)**. Current international guidelines reserve systemic therapy for patients whose disease is refractory to optimized topical regimens or phototherapy, or whose disease location (e.g., palms, soles, extensive body surface) severely impairs quality of life **(Elmets et al., 2020; Nast et al., 2021)**. While systemic agents can induce rapid disease improvement, their use requires careful laboratory and clinical monitoring because of dose-dependent toxicities hepatotoxicity and myelosuppression with methotrexate, nephrotoxicity and hypertension with cyclosporine, and broad infection risk with all immunosuppressants **(Gooderham et al., 2019; Mrowietz et al., 2014)**.

Biological drugs have established themselves as essential treatments for immune system-related chronic inflammatory skin diseases including psoriasis and atopic dermatitis during the last twenty years. The targeted action mechanisms of these agents provide superior efficacy and safety benefits compared to traditional systemic treatments. These drugs target specific inflammatory cytokines with the aim of modulating the immune response that underlies the disease. For example, etanercept and infliximab act on tumor necrosis factor-alpha (TNF- α), while Ustekinumab targets the IL-12/23 pathway, Secukinumab targets the IL-17 pathway, and dupilumab targets the IL-4/13 pathway to regulate the immune response. In recent years, new biological agents such as lebrikizumab have emerged as particularly effective in the treatment of atopic dermatitis and have been approved by the FDA for clinical use in **2024 (Greb et al., 2016; Smith et al., 2024)**. The clinical advantages of biologics are limited by their expensive nature, which makes them inaccessible to patients in low-resource areas at prices higher than \$3000 per year. Numerous patients do not respond to biologics at the beginning and eventually lose their treatment response because their bodies create antibodies against these medications known as immunogenicity. The treatment challenges increase due to rare serious adverse events which include infections and malignancies, but study results have not shown consistent findings

(Reich et al., 2022). The JAK1 inhibitor Upadacitinib stands as a promising oral therapy, which provides alternative treatment for both AD and psoriasis especially for patients who have failed conventional therapies or present with overlapping symptoms. Upadacitinib functions by selectively inhibiting the JAK-STAT signaling pathway, which controls the activity of multiple pro-inflammatory cytokines including IL-4, IL-13, IL-22, and IL-23. Research shows that Upadacitinib demonstrates strong efficacy for treating moderate-to-severe AD by achieving better skin results and lowering patients' itching symptoms (Gori et al., 2024). The medication shows success in treating psoriasiform and spongiotic dermatitis especially when these conditions appear as dupilumab side effects (Wölflle et al., 2024). Most patients can safely use upadacitinib because the medication causes upper respiratory tract infections acne and temporary liver enzyme increases as its most common adverse effects. The occurrence of herpes zoster alongside thromboembolic complications requires patients to receive regular monitoring (AbbVie Inc., 2024). The oral delivery system combined with targeted action makes upadacitinib an essential therapeutic option for managing chronic inflammatory skin diseases among patients who cannot use or react poorly to biologic treatments.

1.3.2. Patient Challenges and Interest in Phytotherapy

The treatment requirements for psoriasis and AD consist of regular application schedules together with continuous medication use and periodic patient monitoring that creates substantial challenges for patient adherence. Patient compliance decreases due to unpleasant side effects including skin discomfort as well as unpleasant cosmetic aspects from ointments. Concerns about the potential side effects of corticosteroids known as corticosteroid phobia acts as a major obstacle for dermatological treatment among patients and their parents. The concerns about corticosteroids result in patients not using their prescribed treatments correctly which leads to poor treatment adherence and harder disease management (Li et al., 2020). The patient population now demonstrates a rising demand for natural treatments and lifestyle approaches as alternatives to conventional pharmacological treatment (Ekor, 2014; Pan et al., 2014). Conventional therapy limitations and high costs together with adverse effects have led patients to explore alternative and complementary medicine specifically through phytotherapy which utilizes medicinal plants and their derivatives for

therapeutic uses. Modern science verifies the effectiveness of phytotherapy through traditional practices and scientific evidence which includes detailed phytochemical analyses and controlled cell-based experiments and randomized clinical trials (Patwardhan et al., 2015). The scientific validation of plant-derived compounds' therapeutic effects on dermatological diseases is supported by multiple studies in the literature. The combination of *Oldenlandia diffusa* with *Rehmannia glutinosa* and *Salvia miltiorrhiza* in multi-component herbal formulations leads to significant PASI score reductions in patients with psoriasis (Deng et al., 2014). Traditional herbal treatment products demonstrate equivalent or better therapeutic outcomes than placebo and conventional pharmaceutical treatments according to research findings (May et al., 2012). The use of nanotechnological systems in herbal compound formulation has improved treatment outcomes by enhancing the bioavailability of these compounds. Research shows that thymoquinone nanoformulations exhibit strong anti-inflammatory properties in psoriasis-like inflammation models (Frontiers in Immunology Editorial Board, 2024). The topical application of shikonin-loaded PLGA nanoparticles demonstrates both accelerated healing of psoriatic lesions and reduced inflammatory responses (Yousaf & Yousaf, 2025). The research evidence demonstrates that phytotherapy exists on both traditional and contemporary scientific grounds.

1.4. Traditional Roots and Scientific Foundations of Phytotherapy

The term “phytotherapy” has not been conceptualized, recently. Traditional medical systems including Traditional Chinese Medicine (TCM), Ayurveda and Unani medicine have integrated phytotherapy as an essential part for thousands of years. Traditional medical practices employed plants to treat skin disorders as well as restore systemic equilibrium and reduce inflammation while boosting immunity (Yuan et al., 2016). For centuries physicians have used *Calendula officinalis* (marigold) and Aloe vera to treat inflamed skin. Ayurvedic practitioners use Neem (*Azadirachta indica*) and Turmeric (*Curcuma longa*) as fundamental remedies for managing eczema and psoriasis conditions. Medieval European medical documents show that physicians employed dandelion, milk thistle and mustard seeds for detoxification and liver health and skin cleansing purposes (Al-Snafi, 2016). Traditional applications exist beyond

cultural legends. Modern pharmacognosy derives its knowledge from traditional uses to identify bioactive compounds which exhibit measurable and reproducible effects on biological systems (**Atanasov et al., 2021**). Plants contain many secondary metabolites which help protect the plants themselves and have medicinal effects in human patients. These include phenolic compounds (e.g., chlorogenic acid, caffeic acid), flavonoids (e.g., quercetin, kaempferol), alkaloids, terpenoids, lignans, and saponins.

These compounds have demonstrated anti-inflammatory, antioxidant, immunomodulatory, antibacterial and antifungal effects which correspond to significant pathways in chronic skin inflammation according to **Mao et al. (2020)** and **Wang et al. (2022)**. Phytochemical compounds show polypharmacology because they simultaneously target several molecular pathways which becomes beneficial for diseases like psoriasis and AD due to their complex redundant immune networks (**Zhou et al., 2016**). The growing acceptance of phytotherapy stems from its mild side effects. The risk associated with all treatments exists, but medicinal plants cause fewer adverse reactions while used in therapeutic doses and standardized **preparations** (**Ekor, 2014**).

Public demand for herbal remedies has risen due to the growing global popularity of the “natural health movement”. Patients tend to choose plant-based treatments because they believe these remedies are more natural and gentler than pharmaceutical options and this aligns with the current wellness and sustainable healthcare trends. Traditional medicines including plant-based remedies form the basis of healthcare for 80% of people worldwide according to the World Health Organization (WHO). The Western world has witnessed a substantial rise in herbal product sales the past twenty years and increasing interest in evidence-based herbal medicine (**WHO, 2013**).

Contemporary phytotherapy exists beyond traditional practices. Modern research supports phytotherapy through clinical trials together with molecular docking studies and in vivo experiments and pharmacokinetic analysis. Scientists are conducting research on plant compounds at the same level as traditional drugs by researching their bioavailability in conjunction with metabolic stability and receptor interaction models (**Daina et al., 2017**). The implementation of HPLC technology together with mass spectrometry and NMR devices has transformed phytochemical analysis by enabling

researchers to standardize plant extracts while identifying their active constituents and molecular targets.

1.4.1 Phytochemical Classes and Mechanisms of Action

Medicinal plants contain numerous secondary metabolites that not only serve to protect the plants themselves but also offer a wide range of pharmacological benefits for human health. These include phenolic compounds (e.g., chlorogenic acid, caffeic acid), flavonoids (e.g., quercetin, kaempferol), alkaloids (e.g., berberine, morphine), terpenoids (e.g., artemisinin, menthol), lignans (e.g., secoisolariciresinol, podophyllotoxin), and saponins (e.g., glycyrrhizin, diosgenin) (**Gómez-Roldán et al., 2023; Abi-Ghannam et al., 2023; Cuciniello et al., 2024**).

These compounds exert anti-inflammatory, antioxidant, immunomodulatory, antibacterial, and antifungal activities mechanisms highly relevant to the pathophysiology of chronic skin inflammation (**Mao et al., 2020; Wang et al., 2022**).

The ability of many phytochemicals to affect multiple molecular pathways simultaneously represents a feature called polypharmacology. The multi-target capability of phytochemicals gives them an advantage over synthetic drugs with single targets when treating diseases such as psoriasis and AD which result from intricate immune network redundancy (**Zhou et al., 2016**).

1.4.2. Global Trends and Scientific Validation of Phytotherapy

The standardization of botanical substances at therapeutic levels has led to their acceptance by the public and scientific community because these substances show less severe side effects than synthetic pharmaceuticals (**Ekor, 2014; Atanasov et al., 2021**). Worldwide herbal-product sales exceeded USD 100 billion because of North American and European consumers who follow natural health practices and seek sustainable healthcare solutions with clean labels (Yuan et al., 2016; Patwardhan et al., 2015). Plant-based remedies serve as the main healthcare solution for treating approximately 80% of the world's population (**WHO, 2013**). Rigorous modern scientific research now supports the popular trend. The combination of HPLC, LC-MS/MS and multidimensional NMR analytical tools has removed confusion about complex extracts by identifying active components which facilitates consistent batch

production (**Atanasov et al., 2021**). The combination of parallel in silico platforms including molecular docking with ADMET prediction and network pharmacology allows researchers to evaluate plant libraries at reduced costs compared to traditional high-throughput assays while identifying leads with promising bioavailability characteristics and receptor affinity (**Daina et al., 2017**).

Many herbal compounds that have been used in traditional medicine for centuries have been supported by scientific research in recent years and have taken their place among evidence-based treatment options in modern medicine. The pharmacological effects of these compounds are not limited to folk medicine practices; they have also been validated through controlled laboratory studies, cell culture experiments, animal models, and clinical research (**Patwardhan et al., 2015**). Today, these herbal agents have been shown to have therapeutic potential in various diseases associated with chronic inflammation, immune system disorders, cellular oxidative stress, and autoimmune responses (**Deng et al., 2014; May et al., 2012; Yousaf & Yousaf, 2025; Catalano, 2016**). These diseases include;

- 1) Cancer: Two chemotherapy agents derived from Pacific yew and Madagascar periwinkle remain used as frontline cancer treatments (**Kingston, 2021; Noble & Cox, 2017**). The medical community continues to study curcumin from turmeric through phase-II trials for colorectal and pancreatic cancer treatment while examining green-tea catechin EGCG as a potential chemo preventive agent (**Hewlings et al., 2020; Gao et al., 2019**).
- 2) Metabolic disorders: The HbA1c-lowering effect of berberine equals that of metformin and ginseng saponins improve insulin sensitivity to the same degree (**Feng et al., 2019; Kim & Park, 2019**).
- 3) Cardiovascular disease: Standardized hawthorn extract improves heart function in patients with mild heart failure and aged-garlic extract shows effectiveness in reducing hypertension and slowing coronary-calcification development (Tauchert, 2012).
- 4) Neuropsychiatry: The antidepressant effects of St. John's wort match those of SSRIs when treating mild to moderate depression while Ginkgo biloba extract EGb 761 helps delay cognitive deterioration in patients with early dementia (**Ng et al., 2017; Hashiguchi et al., 2015**). The combination of strong chemical research with bioinformatics and clinical planning enables phytochemicals to achieve

contemporary pharmacological requirements. The thesis investigates three cultivated plant species including dandelion (*Taraxacum officinale*), milk thistle (*Silybum marianum*) and black mustard (*Brassica nigra*) which traditional herbalism in Europe and the Middle East has utilized for a long time. The same analytical and in silico techniques used to advance paclitaxel, berberine and curcumin will be applied to determine the potential of these plants to manage psoriasis and atopic dermatitis as evidence-based sustainable treatments for chronic inflammatory skin disease.

The positive effects of flavonoids on these disease mechanisms through anti-inflammatory, antioxidant, immunomodulatory, and apoptosis-regulating effects have been demonstrated in numerous studies at both the experimental and clinical levels (PMC, 2023; MDPI, 2023; News-Medical, 2024).

1.5. Therapeutic Potentials and Action Mechanisms of Selected Plants

1.5.1. Milk Thistle (*Silybum marianum*)

Milk thistle is a Mediterranean native flowering plant. The liver-toning plant milk thistle has gained medical attention because its traditional usage revealed multiple healing benefits, which include antioxidant effects alongside anti-inflammatory and antifibrotic and immunomodulatory actions. The bioactive compound silymarin found in milk thistle seeds demonstrates therapeutic potential for liver conditions while also showing effectiveness in treating psoriasis and atopic dermatitis (AD) (Polyak et al., 2010; Post-White et al., 2007).

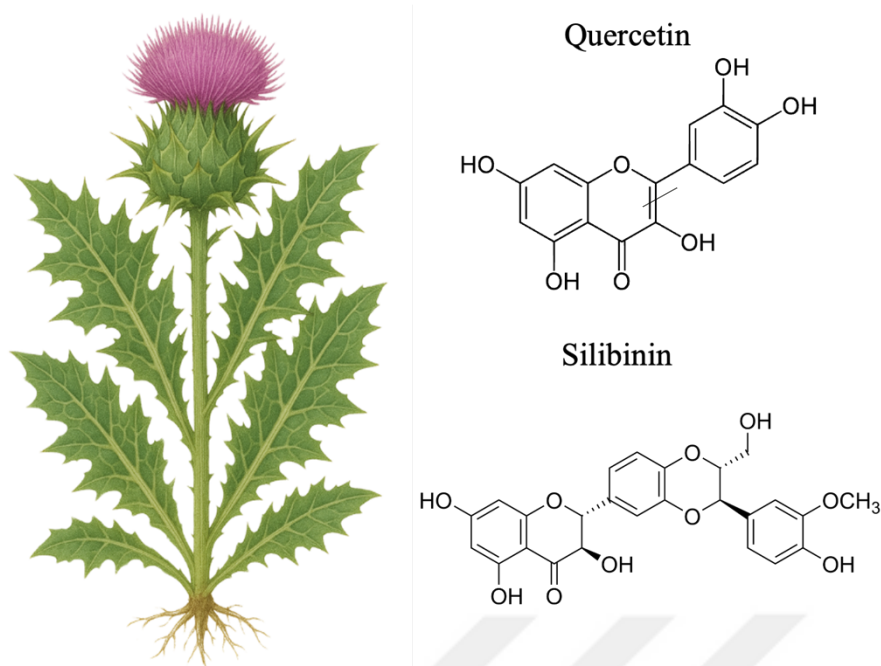


Figure 1.4. Milk thistle (*Silybum marianum*) with the chemical structures of its major bioactive compounds, Silybin and Quercetin, highlighting the plant's flavonoid-based therapeutic potential. *Image generated by AI (ChatGPT o-4-mini).*

Phytochemical Profile

The seeds of milk thistle plants consist of flavonolignans including the primary compound: silymarin, quercetin, luteolin. The compounds exhibit potent radical scavenger capabilities together with membrane-stabilizing effects which defend cells from oxidative and inflammatory injuries according to **Post-White et al. (2007)** and **Polyak et al. (2010)**. Silybin represents the most active pharmacological compound within silymarin because it constitutes 50-60% of its total composition. The major portion of milk thistle's anti-inflammatory and anti-proliferative actions stems from this compound which shows critical importance for treating chronic inflammatory skin disorders (**Katiyar, 2005**). Research conducted in laboratory settings shows positive evidence that milk thistle may serve as an effective treatment for skin inflammation. Silymarin administered both topically and orally in murine models decreased contact dermatitis symptoms together with psoriasiform skin inflammation symptoms by reducing epidermal thickening and erythema and leukocyte infiltration (**Wölflle et al., 2011**).

Silymarin acts as an inhibitor of NF- κ B signaling, STAT3 and p38 MAPK activation, which control the transcription of TNF- α , IL-1 β and COX-2 genes, as well as the production of Th1 and Th17 cytokines, IL-17 and IFN- γ (**Deep & Agarwal, 2010; Katiyar, 2005**).

Silymarin shows particular therapeutic efficacy in the treatment of diseases caused by immune system disorders, as it maintains the balance between pro-inflammatory and anti-inflammatory cytokines. The main pathological process in psoriasis is associated with excessive proliferation of keratinocytes. Silybin arrests the active cell cycle of keratinocytes before triggering the activation of caspase-3, which leads to programmed cell death via mitochondrial pathways (**Agarwal et al., 2003**).

Studies on silybin demonstrate its ability to reduce the expression of cyclin D1 and c-Myc, since these proteins stimulate cell growth, but simultaneously increase the expression of p21 and p53, which contributes to cell cycle arrest and DNA repair (**Kaur et al., 2005**). The study also revealed anti-inflammatory effect of milk thistle. This effect was observed through its ability to act as a cytostatic agent, meaning restoring normal epidermal metabolism. The antioxidant properties of silymarin protect skin cells from damage caused by ultraviolet radiation. In another experimental studies by (**Katiyar, 2005; Wölflé et al., 2011**), silymarin was shown to protect skin cells. This attributed to potential blocking of lipid peroxidation and increasing the activity of SOD and GPx. Another study revealed that silymarin has possessed antioxidant character. Thus, it has high potential of utilization in the treatment of psoriasis by minimizing oxidative stress that causing inflammation and keratinocyte proliferation (**Arora et al., 2010**). The photoprotective effects of silymarin also improve the safety of phototherapy treatments which are commonly used to treat psoriasis (**Deep & Agarwal, 2010**).

Milk thistle is known for its safety profile while maintaining good tolerance among patients who take high doses of the medication without reporting major adverse effects. Gastrointestinal side effects are the most frequent complaints among patients who experience mild nausea and stomach bloating as their primary adverse reactions. Silymarin shows no immunosuppressive or skin-atrophying effects which distinguishes it from standard anti-inflammatory treatments (**Post-White et al., 2007**). The safe use profile and pharmacological potency of this plant make it an ideal choice for dermatological integrative therapy (**Polyak et al., 2010**).

1.5.2. Black Mustard (*Brassica nigra*)

The annual flowering *Brassica nigra* plant known as black mustard belongs to the Brassicaceae (mustard) family. Black mustard seeds have traditionally been used in traditional medicine systems for their anti-inflammatory, antioxidant, and antimicrobial properties even though the plant is better known for its culinary use as a spice and condiment (Fahey et al., 2001; Dinkova-Kostova & Kostov, 2012). Although black mustard seeds have lesser dermatological applications than dandelion and milk thistle its phytochemical profile indicates promising use in chronic skin inflammation management for psoriasis and atopic dermatitis (AD) (Sikorska-Zimny & Beneduce, 2021).

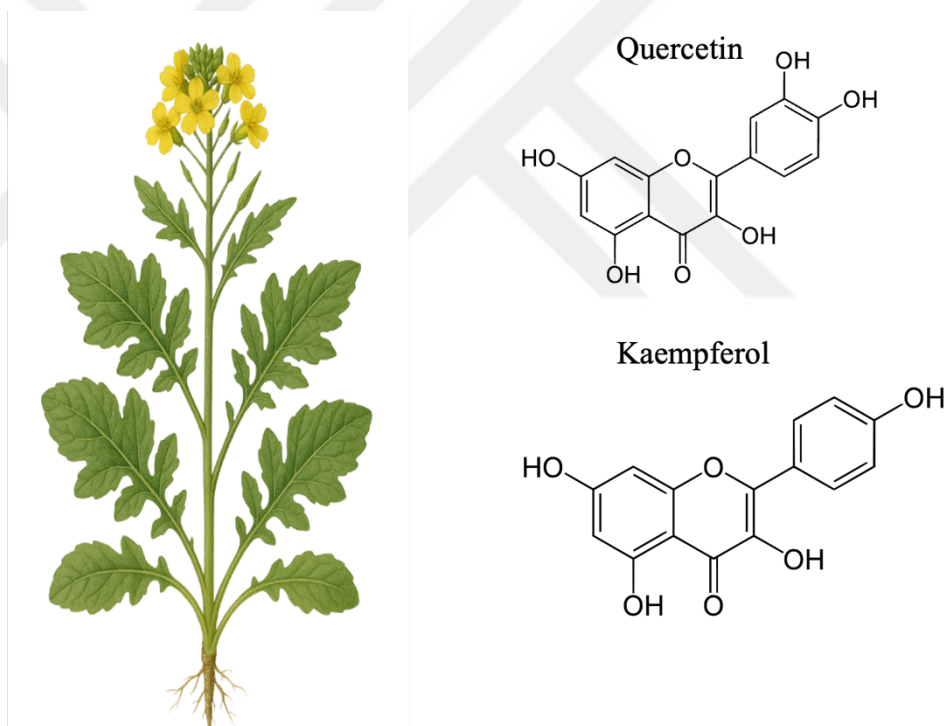


Figure 1.5. Botanical illustration of Black mustard (*Brassica nigra*) displaying its characteristic lobed leaves and clusters of yellow flowers (left), alongside the chemical structures of the flavonoids quercetin (3,5,7,3',4'-pentahydroxyflavone; $C_{15}H_{10}O_7$) and kaempferol (3,5,7,4'-tetrahydroxyflavone; $C_{15}H_{10}O_6$) (right) Image generated by AI (ChatGPT 4-o).

Phytochemical Profile

The two most important compounds in dermatology for their antioxidant and anti-inflammatory effects are sinapic acid and ferulic acid. Research shows these compounds function as ROS scavengers and block pro-inflammatory enzymes including COX-2 and iNOS (Nićiforović & Abramović, 2014; Kaur & Kapoor, 2002). Limited research exists about the specific effects of black mustard seeds on psoriasis or AD, but its systemic anti-inflammatory effects have been confirmed through experimental models. One of the pungent-smelling volatile compounds produced when mustard seeds are crushed, allyl isothiocyanate, is notable for its anti-inflammatory properties. The compound demonstrates anti-inflammatory effects by blocking the nuclear factor kappa B (NF- κ B) signaling pathway. The NF- κ B pathway controls the expression of numerous pro-inflammatory genes so its inhibition functions as a key mechanism to manage systemic and local inflammation. The compound allyl isothiocyanate decreases the production of major inflammatory cytokines TNF- α and IL-6 which restricts inflammatory processes at both cellular and tissue levels. Research shows that this compound directly affects immune system cells by controlling macrophage activation and neutrophil accumulation at inflammation sites to stop excessive immune reactions (Hussain et al., 2019; Xu et al., 2010). Black mustard extracts in murine models of inflammation decrease paw edema along with tissue infiltration and oxidative markers which indicates potential applications in treating chronic inflammatory conditions (Kundu et al., 2010). Skin inflammation intensifies through the process of oxidative stress which damages keratinocytes. The phenolic compound sinapic acid which exists in black mustard demonstrates strong antioxidant properties. The compound performs its antioxidant functions by neutralizing superoxide and hydroxyl radicals and by defending cell membranes from lipid peroxidation and by activating endogenous antioxidant enzymes SOD and catalase (Zdujić et al., 2021). The treatment of human dermal fibroblasts and keratinocytes with sinapic acid leads to decreased oxidative damage along with improved cell viability and decreased expression of inflammatory mediators after UVB or LPS exposure (Sikorska-Zimny & Beneduce, 2021). The impaired skin barrier function in AD and psoriasis makes patients more prone to *Staphylococcus aureus* colonization and other microbial infections. Black mustard shows extensive antimicrobial properties with strength against gram-positive bacteria along with certain fungal

pathogens. Black mustard essential oils and isothiocyanates show evidence of breaking down microbial cell membranes while preventing biofilm **development (Ríos & Recio, 2005; Fahey et al., 2001).**

Traditional medicine has utilized black mustard paste externally for wound healing, but users must apply it with caution due to potential irritation **(Al-Snafi, 2016).** Researchers now investigate the use of liposomal delivery systems because they allow better therapeutic effects with decreased skin irritation **(Vitorino et al., 2014).**

Safety Considerations

Black mustard has been used medicinally and culinarily for many years but applying it topically can produce irritation through burning sensations that demand diluted therapeutic preparations for sensitive skin types **(Al-Snafi, 2016).** The medicinal use of black mustard as food produces safe results, but its bioactive properties require proper measurement in medical treatment **(Dinkova-Kostova & Kostov, 2012).** Black mustard stands as an important yet underdeveloped substance which shows potential for future medical applications especially when used in combination with multiple herbal therapy approaches.

1.5.3. Dandelion (*Taraxacum officinale*)

Dandelion (*Taraxacum officinale*) is a widely distributed perennial flowering plant indigenous to temperate regions of the Northern Hemisphere. Modern scientific studies investigate dandelion because of its established medicinal background and its multiple pharmacological effects which include anti-inflammatory and antioxidative actions as well as hepatoprotective and immunomodulatory properties **(Schütz et al., 2006; Wirngo et al., 2016; Choi et al., 2020).**

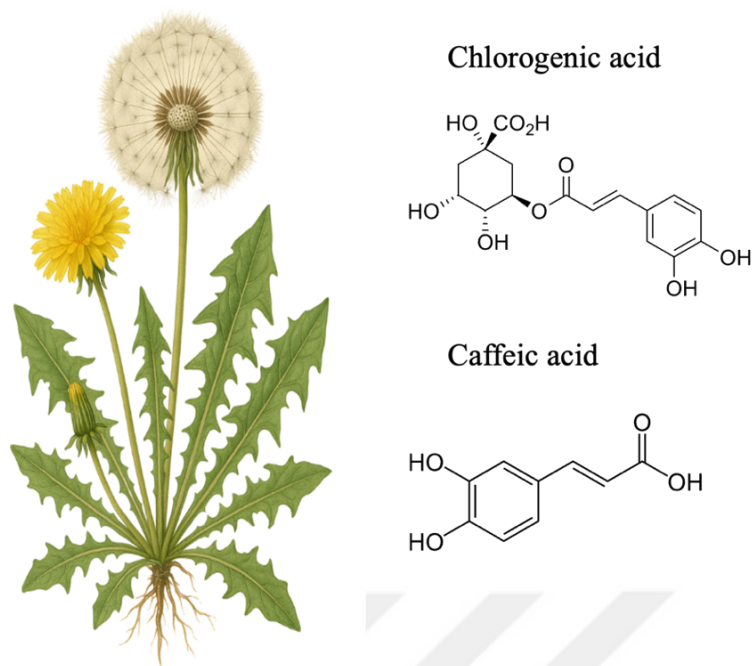


Figure 1.6. It depicts Dandelion (*Taraxacum officinale*) with its yellow flower heads and toothed leaves and spherical seed heads (left) and shows the chemical structures of two phenolic compounds chlorogenic acid (3-O-caffeoylquinic acid; $C_{16}H_{18}O_9$) and caffeic acid (3,4-dihydroxycinnamic acid; $C_9H_8O_4$) (right). The image was generated through AI (ChatGPT o-4-mini).

Phytochemical Profile

Dandelion contains several phenolic acids, such as chlorogenic acid, caffeic acid, quercetin, and luteolin, in its roots, leaves, and flowers. These bioactive compounds are known for their strong antioxidant properties and protect cells from oxidative stress and inflammation (Wirngo et al., 2016; Hu and Kitts, 2005; Martínez et al., 2021). Dandelion contains an abundant amount of chlorogenic acid which stands as the major phenolic acid in the plant. The compound receives extensive research attention because of its powerful anti-inflammatory and antioxidative capabilities. Chlorogenic acid demonstrates strong ability to suppress inflammatory mediators and ROS production which makes it a promising agent for treating inflammatory skin diseases including psoriasis and atopic dermatitis (Schütz et al., 2006; Chen et al., 2022). Laboratory and preclinical examinations have shown dandelion extracts to exhibit strong anti-inflammatory effects through their ability to block NF- κ B activation and decrease TNF- α , IL-1 β and IL-6 cytokines (Jeon et al., 2008; Lee et al., 2020). Caffeic acid shows specific immunomodulatory effects by blocking COX-2 expression that leads

to decreased prostaglandin synthesis and plays an essential role in inflammatory and autoimmune skin diseases (Tsai et al., 2011; Rahman et al., 2019).

The therapeutic benefits of dandelion extracts also stem from quercetin and luteolin which exhibit antiproliferative and apoptotic effects against hyperproliferative keratinocytes. The flavonoids trigger cell cycle stoppage and programmed cell death through caspase-dependent mechanisms and modifications of p21 and p53 proteins which play essential roles in controlling cellular growth and DNA repair processes (Seelinger et al., 2008; Xie et al., 2021). The antioxidant capacity of dandelion extracts provides photoprotective benefits by reducing UV-induced oxidative stress together with lipid peroxidation and subsequent inflammation. Research studies demonstrate that phototherapy treatments combined with dandelion bioactive compounds enhance effectiveness and safety while decreasing typical psoriasis treatment side effects (Wirngo et al., 2016; Zhang et al., 2023).

Dandelion's superior safety profile along with its low side effects at elevated therapeutic levels makes it an appropriate option for integrative dermatological treatment. Patients typically experience minor gastrointestinal side effects such as light nausea when they experience adverse reactions. Dandelion extracts show better advantages as complementary treatments for chronic inflammatory skin conditions because they do not cause immunosuppression or skin atrophy unlike conventional anti-inflammatory drugs (Schütz et al., 2006; Wirngo et al., 2016; Gupta & Sharm, 2024).

1.6. Comparative Evaluation of Selected Medicinal Plants

Dandelion (*Taraxacum officinale*), milk thistle (*Silybum marianum*), and black mustard (*Brassica nigra*) present different botanical and chemical profiles but they all exhibit significant anti-inflammatory and antioxidant properties alongside immunomodulatory effects which help treat psoriasis and atopic dermatitis (AD). The similar and supplementary mechanisms in these plants position them as perfect choices for phytotherapeutic treatment of diseases that have intricate immune pathologies such as chronic inflammatory dermatoses (Atanasov et al., 2021; Zhou et al., 2016). All three plants demonstrate a common ability to control inflammatory responses by affecting molecular inflammatory processes.

NF-κB Inhibition:

The three plants demonstrate NF-κB inhibition through their active compounds taraxasterol in dandelion, silybin in milk thistle and sinapic acid in mustard which prevent NF-κB nuclear relocation and subsequent transcription of TNF-α, IL-1β and IL-6 pro-inflammatory cytokines (Mao et al., 2020; Katiyar, 2005; Nićiforović & Abramović, 2014).

MAPK Pathway Modulation:

Dandelion along with milk thistle effectively block p38 MAPK as well as ERK and JNK phosphorylation which play essential roles in cytokine signaling pathways and keratinocyte activation during psoriasis (Deep & Agarwal, 2010; Polyak et al., 2010).

Th1/Th17 and Th2 Cytokine Suppression:

The three plants show effective activity against various cytokines including IL-17, IFN-γ, IL-4 and IL-13 which makes them suitable for different inflammatory patterns even though psoriasis shows Th1/Th17 dominance and AD features Th2 polarization (Greb et al., 2016; Dainichi et al., 2018). The combination of oxidative stress leads to skin inflammation through keratinocyte damage that enables persistent inflammatory chain reactions. All three plants exhibit robust antioxidant activity: Dandelion produces neutralization effects on superoxide anions while simultaneously boosting glutathione peroxidase activity (Choi et al., 2010). Milk thistle enhances the activity of SOD and catalase and decreases lipid peroxidation (Katiyar, 2005). The sinapic acid in black mustard works directly to neutralize ROS while maintaining cell membrane stability (Nićiforović & Abramović, 2014). The common feature between these plants enables them to control inflammation and repair skin barriers and protect against light exposure which are crucial for treating chronic skin conditions.

Black mustard has minimal research regarding its effects on keratinocytes, but preliminary studies indicate its antioxidant properties could stabilize epidermal cell regeneration (Sikorska-Zimny & Beneduce, 2021). AD patients face higher risks of developing secondary infections from *Staphylococcus aureus* because their compromised skin barriers fail to protect them adequately. Each plant demonstrates different strengths of antimicrobial resistance: Dandelion along with milk thistle shows ability to control gram-positive bacterial growth while simultaneously

decreasing inflammation resulting from microbial signals (**Choi et al., 2010; Post-White et al., 2007**).

Black mustard specifically through its isothiocyanates demonstrates effective antibacterial action against both gram-positive and gram-negative bacteria and shows anti-biofilm activities (**Dinkova-Kostova & Kostov, 2012; Ríos & Recio, 2005**).

These plants work together to achieve microbiome balance restoration which leads to lower infection risks thus becoming essential supplementary advantages for treating inflammatory skin diseases. Phytochemicals demonstrate low toxicity profiles together with minimal systemic side effects which differentiate them from corticosteroids and biologics according to **Ekor (2014)** and **Atanasov et al. (2021)**. Their dual mechanism of action through simultaneous pathway modulation without needing systemic immunosuppression makes them suitable for long-term medication. These agents produce their effects by combining their distinct mechanisms in a synergistic manner. Dandelion's antioxidant properties work with milk thistle's cytokine regulation to enhance its protective effects and black mustard's antimicrobial action provides additional protection according to **Zhou et al. (2016)**.

1.7. Sustainability and Environmental Benefits of Phytotherapy

The increasing prevalence of chronic diseases worldwide has raised concerns about the environmental impact of pharmaceutical production. Traditional pharmaceutical manufacturing processes rely on petroleum resources and generate significant amounts of hazardous waste due to the intensive use of solvents. These extraction methods pollute the environment, cause problems related to climate change, destroy biodiversity, and disrupt natural ecosystems (**Kümmerer et al., 2010**).

Phytotherapy is a method that stands out for its adherence to the principles of "green pharmacy." It utilizes environmentally friendly methods through the use of biodegradable plant products (**Bonaccorso et al., 2021**). The green pharmacy movement embraces herbal medicine because phytotherapy involves utilizing compounds derived from local and edible plants using environmentally friendly cultivation methods and extraction methods.

Taraxacum officinale (dandelion), *Silybum marianum* (milk thistle), and *Brassica nigra* (black mustard) are considered environmentally friendly species suitable for sustainable cultivation. These plants require minimal water and fertilizer inputs and can survive in diverse environmental conditions. Brassica species have been shown to exhibit both drought and salt tolerance (**Zhang et al., 2018**). The agricultural Dandelion is a plant with high agricultural sustainability because it can thrive in low-input, low-pH environments (**Kim et al., 2021**). Milk thistle can also survive in low-nitrogen environments, making it an ideal plant for low-intervention agriculture (**Shakeri et al., 2020**). The unique characteristics of these plants and their ability to survive in diverse conditions contribute to ecological and economic sustainability. The metabolites of these species are more degradable (**Bonacorso et al. (2021)** and **Crinnion (2010)**). In natural aquatic systems, plant compounds degrade faster than synthetic compounds, causing less pollution (**Kümmerer et al., 2018; Beek et al., 2016**). The concept of a bioeconomic-based circular economy can be linked to plant-based medicines because plant extractive waste (roots, stems, and seed pods) can be converted into a variety of sustainable products, from biocompost to biofuels and natural dyes. Milk thistle bark extracted with silymarin becomes a valuable resource for improving soil quality and developing sustainable packaging solutions (**Ali et al., 2020**). Using these methods, pharmaceutical waste is reduced, and manufacturers can implement zero-waste policies in their production facilities (**Heinrich et al., 2020**). The synthesis of phytotherapeutic compounds differs from the synthesis of synthetic drugs due to the use of gentle extraction methods (such as ethanol and supercritical CO₂), few processing steps, and non-toxic catalysts (**Maga & Houghton, 2020**). Extracting medicinal plants is not only environmentally friendly but also provides effective therapeutic outcomes because it can be accomplished in an environmentally friendly, sustainable, and energy-efficient manner. This has the dual benefits of both environmental conservation and health promotion. Herbal medicine promotes the ethical and respectful integration of traditional medical knowledge from trusted sources into modern research (**Heinrich, 2010; Houghton, 2021**). Plants such as dandelion, milk thistle, and mustard seed hold a prominent place not only in European herbal medicine traditions but also in the traditional medical systems of the Middle East, South Asia, and the Mediterranean (**Ekor, 2014**).

1.7.1 Green Chemistry in Herbal Medicine Production

The field of phytotherapeutic research has started to implement green chemistry principles during the recent years. The approach selects environmentally friendly extraction solvents including water and ethanol instead of toxic and harmful solvents. The extraction process becomes more sustainable through reduced energy consumption when it operates at low temperatures. The implementation of solvent recycling systems minimizes resource waste and decreases environmental effects during production. The fundamental principle in product design involves selecting compounds that break down quickly in nature and have low environmental persistence (Bonaccorso et al., 2021; Kümmerer et al., 2018).

Modern green delivery systems based on biodegradable hydrogels and liposomes and plant-based nanocarriers enhance herbal therapy delivery efficiency while remaining environmentally friendly (Maga & Houghton, 2020). Both the World Health Organization (WHO) and European Medicines Agency (EMA) have established guidelines that promote sustainable development of herbal medicinal products. The United Nations Sustainable Development Goals (SDGs) identify sustainable healthcare innovation as a key priority which positions phytotherapy as an appropriate solution for future public health models (WHO, 2013; EMA, 2017; United Nations, 2015).



Figure 1.7. Alignment of the Study with Selected Sustainable Development Goals (SDG 3, 12, 13, and 14)

The research demonstrates its global sustainability alignment through its connection to four Sustainable Development Goals (SDGs) which are illustrated in **Figure 1.7**. The research supports SDG 3 (Good Health and Well-Being) through its development

of phytochemical-based treatments for psoriasis and atopic dermatitis which are two chronic skin diseases with few long-term therapeutic options. The study upholds SDG 12 (Responsible Consumption and Production) principles through its use of renewable plant resources and eco-friendly extraction methods and its minimal dependence on hazardous chemicals. The research supports SDG 13 (Climate Action) through its implementation of low-energy and low-waste processes and biodegradable therapeutic agents. The study supports SDG 14 (Life Below Water) by reducing pharmaceutical residues while promoting biodegradable compounds to protect aquatic ecosystems from enduring chemical pollution.

1.8. Integration of Biotechnology and In Silico Tools in Phytotherapy Research

Natural medicine now operates within a data-driven era where *in silico* methods assist and sometimes replace traditional wet-lab validation methods. The combination of ligand-based target predictors SwissTargetPrediction with docking engines AutoDock Vina/Smina or Glide enables researchers to filter large phytochemical libraries within hours to identify plant metabolites that match disease-relevant protein binding pockets (Trott & Olson, 2010). Mechanistic network-pharmacology platforms (e.g., STITCH, STRING) then place those hits in the context of cytokine and signaling cascades, highlighting multi-target “hub” compounds that may exert broader anti-inflammatory effects (Kanehisa et al., 2023; Szklarczyk et al., 2021). The cheminformatics approach identifies key compounds in dandelion, milk thistle and black mustard which include chlorogenic acid, silybin and sinapic acid that show potential to interact with IL-17A, STAT3 and NF- κ B inflammatory hubs responsible for psoriasis and atopic-dermatitis pathologies. The application of similar *in silico* pipelines to green-tea catechins and licorice flavonoids has revealed strong binding interactions with JAK-STAT and TNF- α signaling nodes (Li et al., 2023; Wang et al., 2022). ADMET filtering performed with SwissADME and pkCSM (Daina et al., 2017) identifies compounds that show both target binding potential and beneficial safety characteristics and pharmacokinetic properties thus guiding laboratory efforts toward promising phytotherapeutic candidates. The combination of omics-level resources including RNA-seq disease signatures in the Connectivity Map and machine-learning QSAR models trained on thousands of anti-psoriatic scaffolds enables researchers to select

phytochemicals which both bind their targets and restore normal gene-expression patterns (**Subramanian et al., 2017; Li et al., 2023**). These biotechnology and computational tools provide an affordable method to transform traditional herbal knowledge into contemporary mechanism-based phytotherapeutic candidates for treating chronic inflammatory skin diseases.



2. AIM OF THE STUDY

The research investigates therapeutic potential of specific phenolic compounds extracted from *Taraxacum officinale* (dandelion), *Silybum marianum* (milk thistle), and *Brassica nigra* (black mustard) against psoriasis and atopic dermatitis molecular targets. The study combines protein–protein interaction (PPI) network analysis with molecular docking and molecular dynamics (MD) simulations. The research follows green chemistry principles alongside sustainable pharmacology and bioeconomic circularity principles. Plant-based therapies demonstrate promise as immunosuppressant alternatives because they possess multi-target effects and are biodegradable and low in toxicity and environmentally friendly for healthcare practices. The research findings will help develop new anti-inflammatory agents that combine effectiveness with ethical sourcing and cost effectiveness and environmental sustainability. This research aims to discover plant-based immunomodulators through computational methods by focusing on molecular targets that play a common role in chronic inflammatory skin diseases such as psoriasis and atopic dermatitis. The identified common target proteins belong to the pathophysiology of these two diseases which should lead to more specific and effective agents that minimize systemic side effects. The approach demonstrates better focus and efficiency than traditional broad-range screening methods. The research employed advanced biotechnological and computational tools which included literature-based target identification and protein–protein interaction (PPI) network construction and structural modeling with AlphaFold and conformational analysis with CABS-flex and molecular docking with Smina and molecular dynamics simulations with GROMACS. This research advances sustainable treatment development by uniting traditional medical understanding with contemporary bioinformatics approaches to achieve United Nations Sustainable Development Goals (SDGs) through this complete methodology.

3. METHODS

3.1. Literature Review and Data Collection

The identification of disease-related protein targets in psoriasis and atopic dermatitis was achieved by conducting a targeted literature review on PubMed, ScienceDirect and the KEGG Pathway Database. The aim was to identify critical inflammatory and immune-related proteins involved in these disorders, based on their role in cytokine signaling and skin barrier dysfunction. The signaling cascades which are well established such as NF- κ B, JAK-STAT and IL-17/IL-23 were further analyzed through computational means.

In parallel, potential therapeutic small molecules were selected through a phytochemical screening of *Taraxacum officinale*, *Silybum marianum*, and *Brassica nigra*. Information on plant-derived bioactive compounds was retrieved from PubChem and DrugBank. The selection criteria included anti-inflammatory, antioxidant and immunomodulatory properties based on peer-reviewed studies. The list of disease-associated proteins and phytochemicals obtained was used as an input for the following: protein interaction network construction, molecular docking, and molecular dynamics simulations.

3.2. Protein-Protein Interaction (PPI) Network Construction and Analysis

A protein-protein interaction (PPI) network was constructed using the STRING database to expand the initial set of disease-related protein targets and gain system-level understanding of their functional relationships. STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) is a database that presents physical and functional interactions between proteins. It integrates data from experimental studies, curated biological databases, gene co-expression levels, genomic context, and text mining of scientific literature to construct protein-protein interaction networks. Each interaction is assigned a confidence score ranging from 0 to 1, with scores $\geq$

0.700 considered high-confidence. This allows users to observe system-level connections between disease-related proteins and gain insights into their biological functions (Szklańczyk et al., 2021).

This step was necessary to reflect the dynamic nature of proteins, which rarely act in isolation but rather function as part of multi-protein complexes and signaling cascades. Dysregulation in one protein may affect the stability or function of the interacting partners, which in turn may alter the disease course. Therefore, the PPI network was used not only to confirm the relevance of known targets but also to extend the protein pool by incorporating first shell interactors with direct functional relevance.

Particular attention was paid to the identification of shared proteins between psoriasis and atopic dermatitis as these may serve as potential dual purpose therapeutic targets.

3.3. Protein Structure Prediction and Optimization

The 3D structures of the proteins obtained from the analyses were obtained using the AlphaFold protein structure database. AlphaFold uses bioinformatics tools such as multiple sequence alignment (MSA), an artificial intelligence-based method for predicting protein structures. This allows for the reliable modeling of three-dimensional structures of proteins that cannot be obtained from experimental data. This method is crucial for modeling proteins that are difficult to analyze in the laboratory (Jumper et al., 2021).

To more accurately reflect biological interactions, both monomer structures and dimer or complex structures, where multiple proteins are combined, were evaluated. Studies with monomeric structures provide direct information about ligand binding sites, while complex structures allow for the study of interaction surfaces between proteins and indirect allosteric effects. Some regions of the structures obtained from AlphaFold had low confidence levels. Therefore, the protein structures were completed using knowledge-based loop modeling and energy-based refinement in the YASARA structure program. Energy minimization was performed on the ligand structures using MOE (Molecular Operating Environment). This process optimized bond geometry, eliminated steric hindrances, and increased local stability. Energy-minimized structures yielded low-energy ligands suitable for protein-ligand interaction analyses. CABS-flex generated multiple conformations for each protein to predict the dynamic

motions of protein structures. This method uses a coarse-grained model to simplify amino acids into interaction sites, enabling the sampling of backbone fluctuations while preserving structural features. The CABS-flex method uses Monte Carlo dynamics to explore the conformational space of a protein using force fields derived from known protein structures (Kurcinski et al., 2019). CABS-flex generated eight conformations for each of the 144 proteins. From these generated conformations, the three structures with the most distinct secondary structures were selected. These structures were used in molecular docking simulations. Applying molecular docking simulations to three different conformations for each protein yielded more biologically meaningful and robust interaction analysis results because it considered multiple binding positions and the protein's secondary structure.

3.4. Preparation of Ligand 3D Structures

The 56 different phytochemical compounds isolated from three medicinal plants analyzed with proven anti-inflammatory properties in traditional medicine and experimental settings: *Taraxacum officinale* (dandelion), *Silybum marianum* (milk thistle), and *Brassica nigra* (black mustard). The selected compounds consisted of phenolic acids, flavonoids, and other polyphenolic components that showed biological activity against skin inflammation and immune dysregulation. The 2D and 3D structural data of the 56 compounds were obtained from PubChem and Drug Bank databases in SDF or MOL file formats. The compounds were entered into MOE for geometry optimization and energy minimization by applying the MMFF94x force field. The optimization process allowed each ligand to achieve a stable low-energy conformation, which served as a prerequisite for molecular docking simulations.

3.5. Molecular Docking Simulations

Smina conducted molecular docking simulations using their AutoDock Vina fork to analyze the binding of phytochemicals to psoriasis and atopic dermatitis target proteins. The molecular docking method identifies optimal ligand positions and binding energies at receptor sites by performing a conformational search and evaluating a physical scoring function. Smina uses its global optimization algorithm with an iterated local search to evaluate van der Waals interactions, hydrogen bonds,

as well as torsional entropy and desolvation effects in its scoring function. The system architecture allows users to modify parameters and create their own scoring functions, making it optimal for large-scale and targeted docking operations (**Koes, Baumgartner, & Camacho, 2013**).

The docking set consisted of 144 different proteins with three conformations generated by CABS-flex, each resulting in 432 protein structures. The docking simulations used 56 phenolic ligands to generate 24,192 protein-ligand pairs. The docking method was based on a blind approach, excluding the choice of any predefined binding site. This strategy allowed the ligands to probe the protein surfaces for orthosteric and allosteric binding sites, leading to a more accurate identification of biologically relevant interactions. A Python script was created to automate the entire docking process. The workflow begins with systematically pairing each of the 432 protein conformations with all 56 ligands to obtain a rich set of docking combinations. The script automatically creates suitable grid cells covering the entire protein surface before performing blind docking for each pair. Smina runs docking simulations for each existing combination. The script collects docking scores and pose files from the results and organizes them into structured output directories for easy access during analysis. The automation system performed large-scale docking simulations with high accuracy and minimized human errors.

3.6. Molecular Dynamics (MD) Simulations

The selected protein-ligand complexes were subjected to molecular dynamics (MD) simulations using GROMACS 2024.2 (**Abraham et al., 2015**) to assess their dynamic stability, structural integrity, and interaction coherence under physiologically similar conditions. The AMBER94 force field consisting of atoms (**Cornell et al., 1995**) was chosen for this study for two main reasons. The force field allows the use of GAFF-derived ligand parameters for 56 phytochemicals since it is cross-consistent (**Wang et al., 2004**). The second reason is that it allows direct comparison with previous molecular dynamics studies of cytokine signaling pathways associated with psoriasis and atopic dermatitis, where AMBER94 was extensively used and RMSD and binding energies were reported (**Acar et al., 2018**). This combination allows for accurate modeling of hydrogen atoms and side chains while maintaining methodological continuity with the existing inflammation literature. Protein–ligand complexes,

selected based on the best binding energies obtained from docking simulations, were placed in a cubic box with a gap of at least 1.0 nm between the protein surface and the edges of the box to prevent interactions with periodic images. The systems were solvated using the Simple Point Charge (SPC) water model (**Berendsen et al., 1987**), and counterions (Na^+ and Cl^-) were added to neutralize the overall charge of the system and simulate physiological salt conditions.

All systems were energy minimized using a steepest descent algorithm with a maximum of 50,000 steps to eliminate unfavorable contacts and reduce the potential energy of the system. The energy-minimized structures were then equilibrated in two successive steps.

1. NVT equilibration (constant number of particles, volume, and temperature) for 100 ps at 300 K using the velocity-rescaling thermostat, which allows temperature coupling with a stochastic element for enhanced stability.
2. NPT equilibration (constant number of particles, pressure, and temperature) for 100 ps at 1 bar using the Berendsen barostat, ensuring the system's pressure was equilibrated and density stabilized before entering the production phase.

For each complex, production runs of 50 nanoseconds were performed under NPT conditions (300 K and 1 bar) with the application of periodic boundary conditions (PBC) in all directions. The leap-frog integration algorithm was used with a 2-femtosecond timestep, ensuring accurate propagation of atomic motions. All bond lengths were constrained using the LINCS algorithm (**Hess et al., 1997**) and the geometry of water molecules was maintained using the SETTLE algorithm (**Miyamoto & Kollman, 1992**). The electrostatic interactions were calculated using the Particle Mesh Ewald (PME) method (**Darden et al., 1993**) with a cutoff of 1.0 nm for both Coulombic and van der Waals interactions. The neighbor lists were updated every 10 steps using the Verlet scheme.

3.6.1. Analysis of MD Simulations

The stability and conformational dynamics of the protein–ligand complexes were assessed using several types of trajectory analyses performed with the built-in GROMACS utilities. The backbone root mean square deviation (RMSD) was calculated to monitor the overall stability of the protein structures during the 50 ns

simulation. The RMSD measurement shows how much the protein backbone atoms deviate from their original positions during the entire simulation period. The stability of the protein structures is reflected in low RMSD values, but high RMSD values reflect both structural flexibility and conformational changes (**Martínez, 2015**). When calculating RMSD in GROMACS, the original reference structure was used for frame alignment according to the following equation (**Abraham et al., 2015**):

$$\text{RMSD} = \sqrt{\frac{1}{N} \sum_{i=1}^N (\mathbf{r}_i(t) - \mathbf{r}_i(0))^2} \quad (3.1)$$

where $\mathbf{r}_i(t)$ represents the coordinates of atom i at simulation time t , $\mathbf{r}_i(0)$ the initial reference position, and N is the total number of atoms analyzed.

The radius of gyration (R_g) was calculated to evaluate the compactness and folding state of protein structures throughout the simulation period. This metric measures how densely the atoms of the protein are packed around its center of mass; thus, consistent R_g values reflect structural compactness and stability, whereas fluctuations indicate conformational variability (**Lobanov et al., 2008**). R_g was calculated using the following formula:

$$R_g = \sqrt{\frac{\sum_{i=1}^N m_i (\mathbf{r}_i - \mathbf{r}_{cm})^2}{\sum_{i=1}^N m_i}} \quad (3.2)$$

where m_i denotes the mass of atom i , $\mathbf{r}_i$ is its position, and $\mathbf{r}_{cm}$ is the center-of-mass position of the structure.

The Solvent Accessible Surface Area (SASA) measures the surface area of biomolecules that solvent molecules can reach. SASA analysis enable to understanding about protein folding processes as well as protein stability and their interactions with surrounding solvent molecules. The simulation shows significant SASA changes which indicate both structural rearrangements and protein–solvent interaction modifications (**Shrake & Rupley, 1973**). The GROMACS software implements the “rolling ball” algorithm to calculate SASA through the following definition:

$$\text{SASA} = \oint \rho(\mathbf{r}) dA \quad (3.3)$$

where $p(r)$ is an indicator function that equals 1 when the solvent probe contacts the molecular surface at position r , and dA represents the surface element over which integration occurs.

The analysis of hydrogen bonds served to determine the stability and duration of molecular bonds between the protein and ligand. The assessment of hydrogen bonds remains crucial for structure-based drug design because these bonds determine both binding affinity and complex stability. The formation of hydrogen bonds was determined through geometrical criteria that established a maximum donor–acceptor distance of 3.5 Å and a maximum hydrogen-donor–acceptor angle of 30 degrees (Bissantz et al., 2010). The built-in gmx hbond tool in GROMACS calculated hydrogen bond numbers and their frequencies and persistence throughout the simulation trajectory to assess protein–ligand interaction durability. The combination of RMSD, Rg, SASA and hydrogen bond calculations offered a complete assessment of both overall structural stability and precise protein–ligand binding stability throughout the simulation period.

3.6.2. Binding Free Energy

Binding free energy analysis has been used to quantify the strength and stability of protein-ligand complexes. It reveals the energetic factors that control ligand binding, allowing researchers to predict and estimate binding affinities. In computational drug discovery and structural biology, MM-PBSA and MM-GBSA are used because they provide an optimal balance between computational speed and accuracy (Genheden & Ryde, 2015). Both MM-PBSA and MM-GBSA decompose the total binding free energy (ΔG_{bind}) into its individual components:

$$\Delta G_{\text{bind}} = \Delta E_{\text{MM}} + \Delta G_{\text{solvation}} - T\Delta S \quad (3.4)$$

where,

ΔE_{MM} includes molecular mechanics energy terms (bonded, electrostatic, and van der Waals interactions). $\Delta G_{\text{solvation}}$ consists of polar and nonpolar contributions to solvation energy, calculated by either the Poisson–Boltzmann (PB) or Generalized Born (GB) methods. $T\Delta S$ represents the entropy change upon binding (Wang et al., 2019).

The main distinction between MM-PBSA and MM-GBSA emerges from their methods for determining the polar component of solvation free energy. The Poisson–Boltzmann (PB) equation in MM-PBSA provides a rigorous approach to model the solvent as a continuum which solves the electrostatic potential around the solute with high accuracy at the expense of increased computational cost (Kollman et al., 2000). The analytical Generalized Born model in MM-GBSA provides fast computational speed with acceptable accuracy which makes it appropriate for studying numerous complexes and extended trajectories (**Onufriev et al., 2000; Hou et al., 2011**).

The analysis used trajectory frames which corresponded to stable regions that were identified from backbone RMSD plots. The simulation trajectories were limited to the equilibrated periods which displayed stable and minimal RMSD value fluctuations for protein–ligand complexes. The MM-PBSA binding free energy calculation was run only on the equilibrated trajectory segments to obtain dependable and representative ligand binding affinity and complex stability estimates (**Genheden & Ryde, 2015; Wang et al., 2019**).

4. RESULTS

4.1. Literature Review and Data Collection

In this study, a detailed literature review was conducted to identify proteins associated with psoriasis and atopic dermatitis (AD), aiming to distinguish between shared and disease-specific molecular components. Both psoriasis and AD are chronic, immune-mediated skin conditions characterized by distinct immunological mechanisms; however, recent research reveals an increasing recognition of overlapping pathways in their pathogenesis. Traditionally, psoriasis has been associated with a Th1/Th17-driven response, whereas AD has been dominated by a Th2-skewed immune profile. Despite these canonical differences, chronic or severe stages of AD often show activation of Th1 and Th17 signaling, narrowing the immunological gap between the two diseases (**Guttman-Yassky et al., 2018**). The convergence of these diseases has led to the identification of several common molecular targets. JAK1 functions as a central component of the JAK/STAT pathway to signal various interleukins, simultaneously contributing to the development of both psoriasis and Alzheimer's disease (**Garcia-Melendo et al., 2021; Silverberg & Fonacier, 2021**). IL-12/IL-23 axis components IL12B, IL12RB1, IL23A, and IL23R regulate Th1 and Th17 responses in both diseases, according to **Cohen et al. (2020)** and **Garcia-Melendo et al. (2021)**. IL-17A and its receptor IL-17RC exhibit elevated levels in chronic AD subtypes and play an important role in psoriasis-associated epithelial inflammation, suggesting their broader importance in cutaneous immunopathology. The molecules listed in **Table 4.1** are frequently reported in the literature and represent potential therapeutic targets for future therapies that may benefit patients with both diseases. The review identified disease-specific molecules, demonstrating how each disease maintains its unique immunological characteristics. IFNG, IL1B, TNF, IL6, and IL6R proteins showed a strong association with psoriasis but not with Alzheimer's disease, according to **Smith and Barker (2020)**, **Wang Zhao (2020)**, **Lee and Lim (2020)**, and **Nguyễn et al. (2022)**. IL10RA, IL13, IL13RA2, SFN and IL22RA1 are primarily involved in the pathogenesis of Alzheimer's disease, according to **Liu et al. (2019)**, **Guttman-Yassky et al. (2018)** and **Yong et al. (2021)** These disease-specific protein

profiles are detailed in **Table 4.2**, offering valuable insight into differential diagnosis and targeted drug development opportunities.

Table 4.1. Shared Primary Proteins Identified in Both Psoriasis and Atopic Dermatitis Based on Literature

Proteins	Psoriasis	Atopic Dermatitis	Reference
JAK1	Present in both	Present in both	(Garcia-Melendo et al., 2021)
IL12B	Present in both	Present in both	(Cohen et al., 2020)
IL12RBI	Present in both	Present in both	(Cohen et al., 2020)
IL23R	Present in both	Present in both	(Cohen et al., 2020)
IL23A	Present in both	Present in both	(Garcia-Melendo et al., 2021)
IL17A	Present in both	Present in both	(Cohen et al., 2020; Garcia-Melendo et al., 2021)
IL17RC	Present in both	Present in both	(Cohen et al., 2020)

Table 4.2. Primary Proteins Identified in Atopic Dermatitis and Psoriasis Pathways Based on Literature Review

Protein	Atopic Dermatitis	Psoriasis	References
IFNG		✓	Smith & Barker, 2020
IFNGR1		✓	Johnson et al., 2019
IL10RA	✓		Guttman-Yassky et al., 2018
IL13	✓		Liu et al., 2019
IL13RA2	✓		Liu et al., 2019
IL1B		✓	Wang & Zhao, 2020
IL22	✓		Guttman-Yassky et al., 2018
IL22RA1	✓		Guttman-Yassky et al., 2018
IL6		✓	Nguyễn et al., 2022
IL6R		✓	Nguyễn et al., 2022
JAK1	✓		Silverberg & Fonacier, 2021
JAK2	✓		Silverberg & Fonacier, 2021
SFN	✓		Yong et al., 2021
TNF		✓	Lee & Lim, 2020

4.2. Protein–Protein Interaction (PPI) Network Analysis

The PPI network analysis using STRING database was performed to understand the molecular relationships and functional interactions among the proteins involved in

atopic dermatitis (AD) and psoriasis. The network analysis was performed based on disease-specific and shared proteins identified in the literature review to visualize the signaling pathways and the central nodes of immune system. The network analysis of the included proteins showed a high degree of connectivity which suggested the coordinated activity and synergistic effects of immunological processes. Most of the proteins involved in AD and psoriasis are not working in isolation but they are interconnected in a signaling web that could influence the development and severity of the diseases. To investigate the biological significance of the network, pathway enrichment analysis was performed using the KEGG and Gene Ontology (GO) annotations integrated in STRING.

This analysis was to determine the key signaling pathways in which the network proteins are overrepresented. The results indicated that there were several immune-related pathways that were enriched such as cytokine-mediated signaling, T cell differentiation, NF- κ B signaling, and especially JAK/STAT signaling pathway, which was the most significantly enriched functional module. Specifically, JAK1, JAK2, IL6, IL6R, IL10RA, IL12B, IL12RB1, IL23A, IL23R, IFNG, and STAT3 were highly related to the JAK/STAT signaling pathway.

This pathway plays a crucial role in transferring signals from extracellular cytokines to the nucleus to influence the expression of genes involved in immune activation, inflammation, cell survival, and proliferation. The dysregulation of this pathway is well known to be involved in the pathogenesis of chronic inflammatory diseases and is a validated target for therapeutic intervention in both AD and psoriasis. Furthermore, IL4, IL13, TNF, and TYK2 were among the proteins enriched in the cytokine-mediated signaling pathway. This pathway encompasses a broad range of cytokine-receptor interactions that modulate immune cell communication, differentiation, and activation—processes that are important in the pathogenesis of both diseases.

Another significant cluster of proteins, including IL12B, IL12RB1, IL23A, IL23R, and IL17A, was linked to T cell differentiation processes. These molecules are central to the functional polarization of T-helper subsets such as Th1, Th2, and Th17 cells. Their presence in the network supports the immunological complexity and overlapping features of psoriasis and chronic forms of AD, in which Th1 and Th17 activity becomes more prominent alongside the typical Th2 response.

Lastly, the NF- κ B signaling pathway, a major regulatory cascade responsible for controlling the transcription of pro-inflammatory genes, was enriched by proteins such as TNF and IL1B. Activation of NF- κ B contributes to the persistent inflammation and immune cell infiltration seen in lesional skin of both diseases, reinforcing its importance as a common pathophysiological mechanism.

Figure shows node sizes proportional to degree centrality, which identifies hub proteins and node colors differentiate between disease-specific and condition-shared proteins. The visualization demonstrates how immune pathways connect to each other while revealing essential regulatory proteins that could become future therapeutic targets.

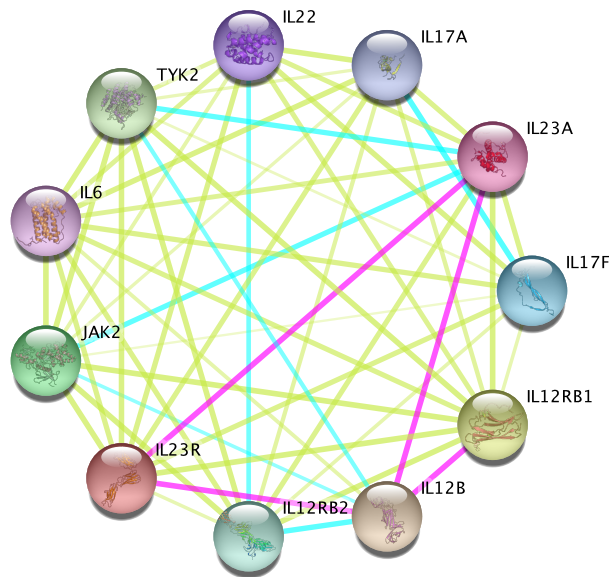


Figure 4.1. Protein–protein interaction network of only literature-validated primary proteins visualized using Cytoscape. Edge colors represent interaction evidence: green (gene neighborhood), cyan (database), and magenta (experimentally determined).

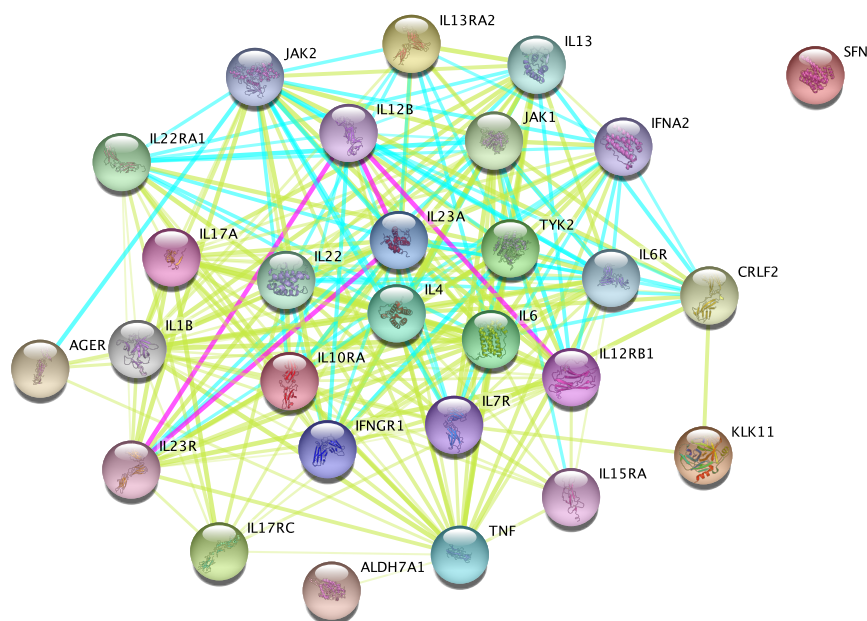


Figure 4.2. Extended interaction network comprising both primary and STRING-enriched secondary proteins. Edge colors reflect interaction evidence: green (gene neighborhood), cyan (database), and magenta (experimentally determined).

4.3. Generation of Alternative Protein Structures (CABS-flex)

The extended pool of proteins from Protein–Protein Interaction (PPI) network analysis underwent molecular dynamics simulations to gain better structural understanding of proteins linked to psoriasis and atopic dermatitis.

The extensive method enabled to evaluate both proteins identified in literature and those proteins that were indirectly linked to the network. The server produced ten different protein conformations for each protein and evaluated all generated conformations before choosing three models which displayed the most significant differences in secondary structure elements including α -helices, β -sheets and loop flexibility for subsequent molecular docking analysis. The selected conformers are shown in **Figure 4.3**

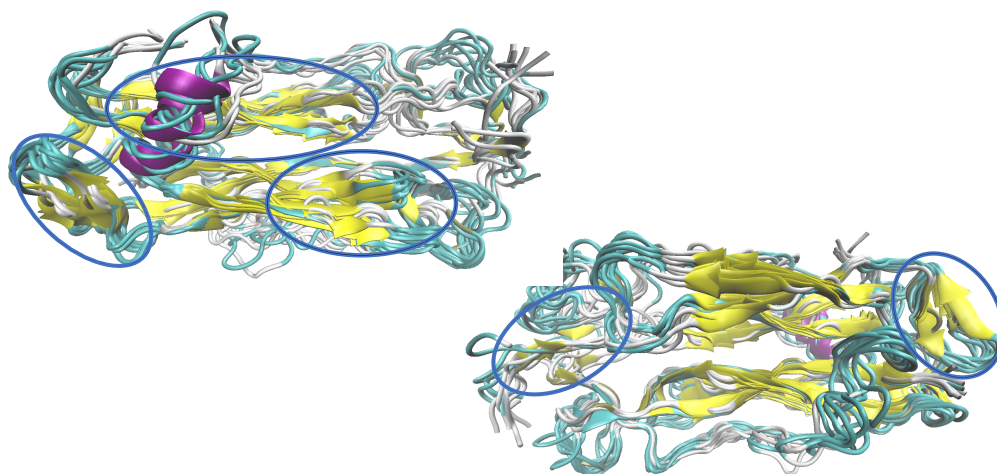


Figure 4.3. Ten conformations of the IL17A protein were generated by CABS-flex. The highlighted regions represent structural variations across different conformations.

4.4. Molecular Docking Simulations Analysis

The purpose of performing molecular docking simulations in this study was evaluating binding tendencies of phytochemicals and drug-like molecules toward target proteins implicated in psoriasis and AD. The analysis of binding energies and interaction patterns served to identify potential inhibitors and therapeutic candidates.

The docking simulations were performed on pool of proteins that were obtained from protein–protein interaction (PPI) network expansion. The total number of protein models reached 432 because 144 proteins were each represented by three conformations. The total number of docking poses obtained was 241,920 (432 proteins x 56 ligands x 10 poses). This approach ensured that various conformers of the proteins were include in the study and the binding of ligands onto each conformer was analyzed.

The Smina docking simulation tool performed molecular docking simulations through its improved AutoDock Vina uses with binding affinity above the threshold value of -10.0 kcal/mol were discarded to find a balance between reduction of computational workload and the accuracy of the study.

Some of the compounds displayed multiple interactions with various proteins according to the analysis The docking results demonstrated that Luteolin 7-O-[(β -D-glucuronic acid)] along with Quercetin-3,7-O-B-D-diglucoside, Kaempferol-3,7-

diglucoside, and Apigenin-7-O-glucuronide interacted with numerous proteins. This result demonstrated that compounds in the study bound to multiple target proteins associated with both psoriasis and atopic dermatitis based on their broad-spectrum binding potential. The bubble plots demonstrated the top target proteins and most consistent ligands which helped for pick suitable complexes for detailed analysis and molecular dynamics simulations.

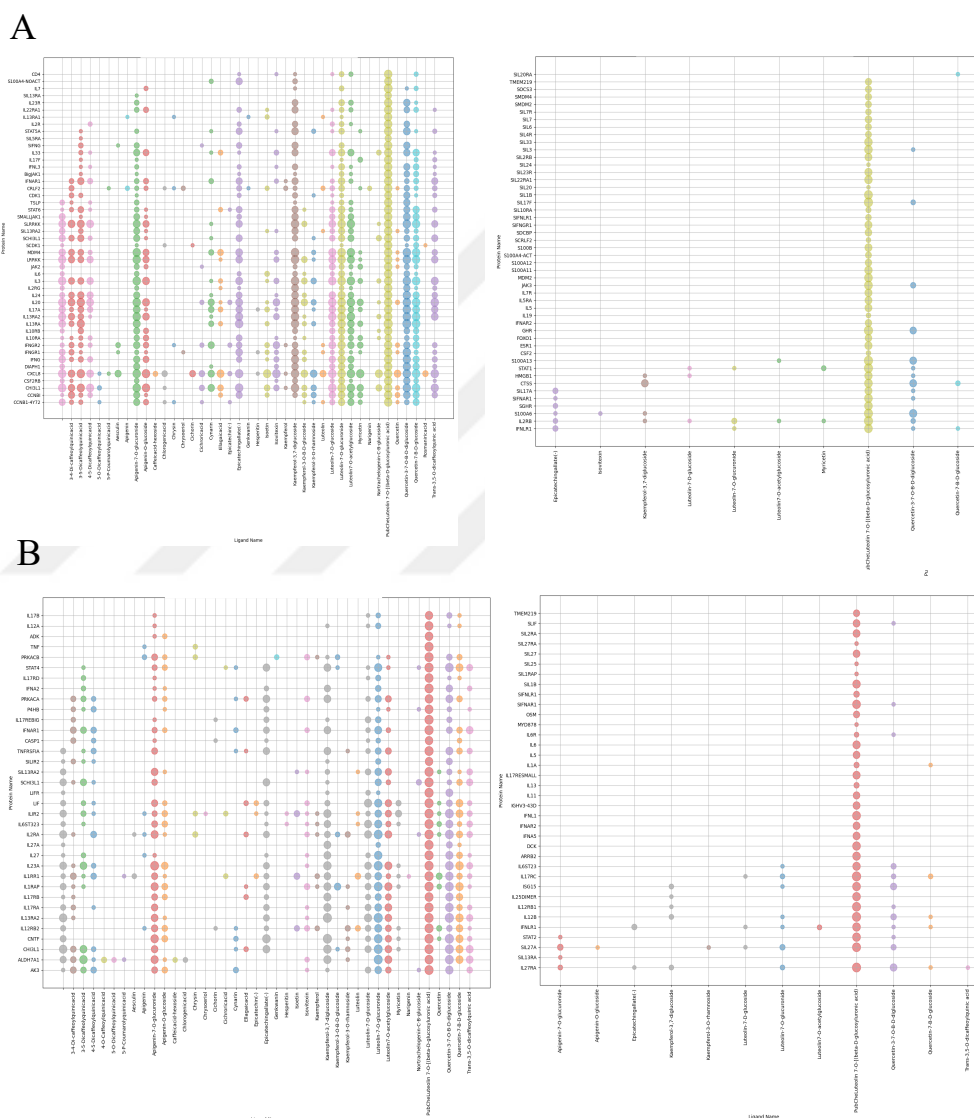


Figure 4.4. Bubble plot representation of frequently interacting ligands with target proteins (A) Atopic dermatitis-associated proteins and their interacting ligands. (B) Psoriasis-associated proteins and their interacting ligand. Bubble size indicates the number of docking poses in which a given ligand interacted with a particular protein. Only ligand-protein complexes with binding affinities below -10 kcal/mol were included in the visualization to highlight the most relevant and potentially effective interactions.

Following the bubble plot analysis, protein structures that exhibited limited interactions with ligands were excluded from further consideration. As illustrated in the bubble plots (**Figure 4.4**), certain proteins were found to interact with only a small number of ligands and therefore were omitted from subsequent evaluations. This filtering step allowed focusing on protein-ligand interactions with greater pharmacological relevance and therapeutic potential.

Moreover, the protein-protein interaction (PPI) network analysis revealed that some proteins initially identified as primary targets for one disease also appeared as secondary yet functionally significant targets in the context of the other disease, once the protein pool was expanded. This finding confirmed the presence of shared molecular components in the signaling pathways of both psoriasis and atopic dermatitis. Notably, these shared proteins tended to interact more frequently with high-affinity ligands, suggesting their potential as dual-purpose therapeutic targets.

Based on these insights, ligand-protein complexes characterized by both strong binding affinity (below -10 kcal/mol) and frequent interactions particularly involving disease-relevant and shared proteins—were prioritized. The final set of selected complexes was presented in **Table B-1 (Appendix)** and was subjected to MD simulations for further structural and dynamic evaluation.

As a result of the successive filtering steps, a total of 120 protein-ligand complexes were identified based on binding affinity and interaction frequency criteria. To determine which ligands were more frequently involved in these complexes and to assess their potential therapeutic relevance a ligand occurrence frequency analysis was conducted. This analysis aimed to identify the most recurrent ligands among the selected complexes, highlighting compounds with notable structural compatibility, binding flexibility, and multi-target interaction potential.

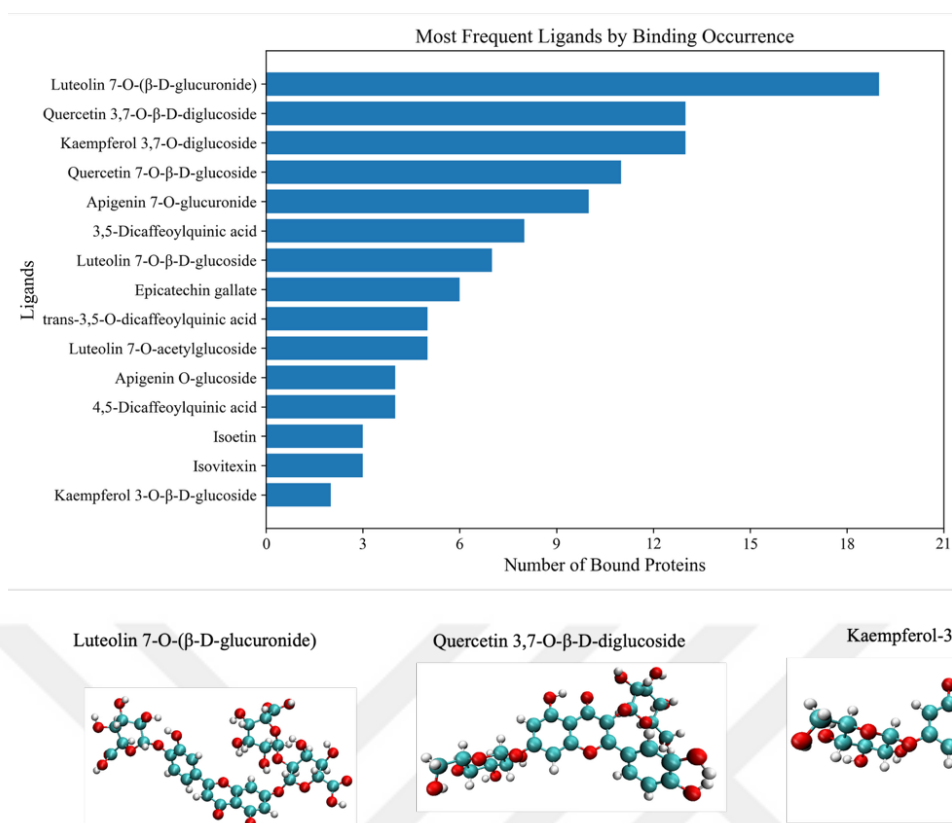


Figure 4.5. Figure illustrates the recurrence frequencies of ligands across the final 120 complexes.

According to the results,, Luteolin 7-O-(β-D-glucuronide) formed the highest number of complexes (19) with various protein targets, indicating its strong and versatile binding profile. This was followed by Quercetin 3,7-O-β-D-diglucoside and Kaempferol 3,7-O-diglucoside, each involved in 13 complexes. Additionally, Quercetin 7-O-β-D-glucoside and Apigenin 7-O-glucuronide participated in 11 and 10 complexes, respectively.

4.5. Molecular Dynamics Simulations Analysis

4.5.1. RMSD Analysis

RMSD analysis monitored the structural variations of proteins and ligands across the entire duration of MD simulations. Multiple protein-ligand complexes displayed different degrees of structural variability during the first 30 nanoseconds of simulation based on their backbone RMSD analysis. A few systems achieved RMSD stabilization

during the last 20 ns thus indicating that some complexes established conformational equilibrium while the system was under dynamic condition reference positions and provides insights into the overall structural stability of the system.

Notably, complexes containing Luteolin-7-O- β -D glucuronide, Quercetin-3,7-O- β -D-diglucoside, Apigenin-7-O-glucuronide, Kaempferol-3-O- β -D-glucoside, and Myricetin displayed relatively lower RMSD fluctuations in the protein structures. These findings suggest that these ligands may support structural integrity by binding in a conformationally compatible manner.

Ligand RMSD analysis was used to determine whether the compounds maintained their positions within the binding site throughout the simulation. In general, many ligands remained within a relatively narrow positional range, with consistently low RMSD values. In particular, ligands such as Epicatechin, Luteolin-7-O-glucoside, Apigenin-7-O-glucoside, Quercetin-7-O- β -D-glucoside, Luteolin-7-O- β -D-glucuronide, Kaempferol-3,7-diglucoside, Myricetin, Silybin, and Luteolin-7-O- β -D-glucoside showed limited deviation and appeared to retain their binding positions throughout the simulations.

Nevertheless, some ligands exhibited noticeable fluctuations in RMSD depending on the protein environment. These variations could be attributed to partial misalignment within the binding site, conformational adjustments, or the intrinsic flexibility of the complex. In such systems, however, a tendency toward stabilization was still observed in the later stages of the simulations.

When protein and ligand RMSD results were evaluated together, a subset of ligands demonstrated relatively stable behavior in both components. Notably, Luteolin-7-O-glucuronide, Myricetin, Apigenin derivatives, and Kaempferol glycosides emerged as ligands that preserved their binding poses while also minimizing structural perturbations in the protein. RMSD profiles of all protein and ligand systems were presented in **Appendix Figure E-1** (protein RMSD) and **Appendix Figure F-1** (ligand RMSD).

4.5.2. Solvent Accessible Surface Area (SASA) Analysis

The Solvent Accessible Surface Area (SASA) analysis evaluated protein surface exposure to solvent throughout the simulation period. The analysis revealed how protein-ligand complexes interact with solvents through dynamic solvation behavior.

The simulated protein–ligand complexes showed a steady reduction in Solvent Accessible Surface Area (SASA) values throughout the simulation period which indicated that protein structures became more compact and closed. The decrease in SASA values was not significant in all systems but a small downward trend was observed in most of the simulations. These findings suggest that protein-ligand interactions may promote structural tightening and local rearrangement of the protein surface upon binding.

It is suggested that ligand binding, particularly around the binding region, may contribute to partial shielding of the protein surface from the solvent, thereby reducing the accessible surface area (Li et al. (2023), Zhou et al. (2018), Singh & Patel (2022)). SASA profiles of all simulated complexes are provided in **Appendix Figure G-1**.

4.5.3. Radius of Gyration (Rg) Analysis

The Radius of Gyration (Rg) analysis examined the structural compactness of proteins across the entire simulation period. Most complexes maintained their folded structures because Rg values showed minimal changes during the simulation period. The simulations revealed that only a few systems displayed minor variations in Rg values throughout the entire simulation period. The analysis showed that particular ligands produced small effects on how proteins maintained their compactness.

The Rg values of IL17A complexed with 4,5-dicaffeoylquinic acid were lower than other systems indicating a possible compact protein structure. Luteolin-7-O-acetylglucoside bound to IL23R resulted in Rg values that decreased slightly which could indicate the stabilization of a more folded protein structure. The Rg values increased slightly in systems that contained Isovitexin when compared to other systems. The complexes containing 3,4-dicaffeoylquinic acid with IL10RA and 3,5-

dicaFFEoylquinic acid with JAK1 showed significant Rg value fluctuations, which indicated restricted protein conformational changes due to ligand binding.

The Rg analysis showed that most protein-ligand complexes maintained their structural compactness during the entire simulation period. The ligand-dependent changes in compactness were moderate yet showed no consistent pattern throughout all systems. The Rg profiles of all simulated complexes are shown in **Appendix Figure H-1**.

4.5.4. Hydrogen Bond (H-Bond) Analysis

The stability and continuity of interactions in the binding regions of protein–ligand complexes were evaluated by performing hydrogen bond analyses between protein and ligand atoms throughout the molecular dynamics simulations. The average number of hydrogen bonds formed per complex during the simulations was calculated to assess the interaction profiles.

The results indicate that some ligands formed a higher number of consistent hydrogen bonds with various target proteins. Luteolin 7-O-(β -D-glucuronide) and Quercetin 3,7-O- β -D-diglucoside were prominent, showing elevated average hydrogen bond counts across multiple targets. Luteolin 7-O-(β -D-glucuronide) formed approximately 6–10 hydrogen bonds on average with proteins such as IFNG, JAK1, IL17A, IL10RA, IL23R, and IL12B. Similarly, Quercetin 3,7-O- β -D-diglucoside showed average hydrogen bond counts exceeding 5 with targets including IL17A, IFNGR1, IL12B, and SJAK1.

Other flavonoid derivatives such as Kaempferol 3,7-O-diglucoside, Apigenin 7-O-glucuronide, Luteolin 7-O- β -D-glucoside, Epicatechin gallate, Myricetin, and Silybin demonstrated moderate interactions with proteins such as IL10RA, IL12B, JAK2, and IL6. The numbers of average hydrogen bonds varied between 3.5 and 5.5.

On the other hand, some ligand-protein complexes exhibited relatively lower hydrogen bond averages in the range of 2.0–3.5. This may suggest fewer contact points or less optimized binding conformations. Compounds such as Isovitexin, Apigenin O-glucoside, Aesculin, and certain dicaFFEoylquinic acid derivatives were among the ligands with lower hydrogen bond averages.

Overall, this analysis provided insight into the extent and duration of hydrogen bond formation in each protein-ligand complex during the simulations. Detailed of the average hydrogen bond counts were presented in **Appendix Table C-1**.

4.5.5. Binding Free Energy (ΔG) Analysis

Following molecular dynamics simulations, MM/GBSA calculations were performed to evaluate the binding free energies (ΔG) of each protein-ligand complex, allowing a comparative assessment of binding affinities. The following sections provide a detailed discussion on the average ΔG values for each target protein-ligand complex.

IL12B

Among all ligands tested against IL12B, Luteolin-7-O-glucoside exhibited the most favorable binding affinity with a ΔG_{total} of -62.95 kcal/mol. This was followed by Quercetin 3,7-O- β -D-diglucoside and Kaempferol-3,7-diglucoside, with ΔG values of -49.60 and -47.83 kcal/mol, respectively. These values indicate strong and potentially stable interactions between these flavonoids and the IL12B binding site.

IL10RA

Luteolin 7-O-(β -D-glucuronide) showed the strongest interaction with IL10RA, reaching a ΔG_{total} of -61.64 kcal/mol. Several other ligands, including 3,4-Dicaffeoylquinic acid (-61.02 kcal/mol), Kaempferol-3-O- β -D-glucoside, and Kaempferol-3,7-diglucoside (both around -57 kcal/mol) also demonstrated high binding affinities. Additionally, Quercetin 3,7-O- β -D-diglucoside, Apigenin 7-O-glucuronide, and Luteolin-7-O-acetylglucoside were notable with moderate ΔG values between -49.7 and -42.7 kcal/mol.

IL23R

Luteolin-7-O-glucoside was the top performer against IL23R, with a ΔG_{total} of -59.09 kcal/mol. It was followed by Luteolin-7-O-acetylglucoside and Kaempferol-3,7-diglucoside, with ΔG values around -35 kcal/mol, while Apigenin 7-O-glucuronide and Quercetin 3,7-O- β -D-diglucoside showed moderate binding.

JAK1 (Monomeric and Dimeric)

In the dimeric form, Epicatechin gallate showed the most favorable ΔG_{total} (-55.92 kcal/mol), followed by Luteolin-7-O-glucoside (-54.01 kcal/mol) and Quercetin-7-O- β -D-glucoside (-49.16 kcal/mol).

In the monomeric form, Quercetin 3,7-O- β -D-diglucoside and Kaempferol stood out with ΔG values of -48.88 and -45.66 kcal/mol, respectively. Other ligands such as Apigenin 7-O-glucuronide, 3,5-Dicaffeoylquinic acid, and Luteolin 7-O-(β -D-glucuronide) displayed moderately favorable interactions.

JAK2

Luteolin 7-O- β -D-glucoside and Luteolin 7-O-(β -D-glucuronide) were among the strongest ligands for JAK2, with ΔG values of -54.01 and -52.21 kcal/mol, respectively. Moderate binding was also observed for Apigenin 7-O-glucuronide, Quercetin 3,7-O- β -D-diglucoside, and Myricetin, typically ranging from -42.1 to -36.8 kcal/mol.

IL23A

The best interaction was seen with Apigenin 7-O-glucuronide (-52.57 kcal/mol), followed by Isovitexin, Quercetin 3,7-O- β -D-diglucoside, and Myricetin, all showing ΔG values between -38.5 and -31.1 kcal/mol. Ligands such as Luteolin-7-O-glucoside and Kaempferol derivatives had lower but still relevant affinities.

IL6 and IL6 Complex

In IL6 complexes, Luteolin-7-O-glucoside was again a top ligand with -51.79 kcal/mol, while Kaempferol-3,7-diglucoside, Isoetin, and Silibinin ranged between -31.0 and -18.2 kcal/mol. The lowest binding was observed with Epicatechin gallate (-7.95 kcal/mol), indicating weaker interaction with this target.

IL17A and IL17A Complex

Luteolin-7-O-glucoside demonstrated strong and consistent binding across multiple conformers, with ΔG values of -51.27, -38.52, and -34.46 kcal/mol. Other top ligands included Quercetin 3,7-O- β -D-diglucoside, Quercetin-7-O- β -D-glucoside, 4,5-Dicaffeoylquinic acid, and Epicatechin gallate, with values generally ranging from -50 to -30 kcal/mol.

IFNG and IFNG Complex

Luteolin-7-O-glucoside and Quercetin 3,7-O- β -D-diglucoside were again among the most stable ligands for IFNG, with ΔG values of -46.4 and -47.2 kcal/mol, respectively. Moderate binding was seen for Cichoric acid, Apigenin 7-O-glucuronide, and Aesculin (-38 to -30 kcal/mol).

IFNGR1

IFNGR1 also exhibited interactions with several ligands. The most favorable ΔG_{total} was observed with Luteolin-7-O-glucoside (-28.08 kcal/mol), followed closely by PubCheLuteolin 7-O (-27.89 kcal/mol). These values suggest moderate affinity, although lower compared to the complexed form. The data indicate that Luteolin-based structures may retain selective interaction potential even in the non-complexed state of IFNGR1.

IFNGR1 Complex

A wide variety of ligands interacted with IFNGR1 in its complexed form. Luteolin 7-O- β -D-glucoside showed strong binding (-48.80 kcal/mol), while Kaempferol-3,7-diglucoside, Quercetin 3,7-O- β -D-diglucoside, Aesculin, and Apigenin 7-O-glucuronide followed with values between -41 and -30 kcal/mol. Lower affinities were observed for Ellagic acid, Isoetin, and Luteolin.

TNF, IL1B, IL12RBI, IL17RC

These targets exhibited overall weaker binding. Luteolin-7-O-glucoside with TNF showed a relatively high ΔG_{total} (-46.64 kcal/mol), followed by Apigenin, Quercetin, and Naringenin. In IL1B, Silibinin and 3,5-Dicaffeoylquinic acid showed moderate interaction. IL12RBI and IL17RC showed weaker overall binding, with top ligands like Kaempferol-3,7-diglucoside and Quercetin 3,7-O- β -D-diglucoside yielding ΔG values mostly above -30 kcal/mol

5. DISCUSSION

This study employed a multi-step computational approach to evaluate the therapeutic potential of flavonoid derivatives in modulating inflammatory pathways relevant to psoriasis and atopic dermatitis (AD). The findings collectively provide insight into how phytochemicals may exert modulatory effects through multi-target interactions, structural stabilization, and persistent binding patterns.

The construction of the protein–protein interaction (PPI) network revealed a dense interaction web among psoriasis- and AD-associated targets, indicating a high degree of molecular interdependence. Pathway enrichment analysis via STRING confirmed that the selected proteins are primarily involved in critical immune-related signaling cascades, particularly the JAK/STAT, cytokine-mediated signaling, T cell differentiation, and NF- κ B pathways. Central proteins such as JAK1, IL10RA, IL23A, IL17A, and STAT3 were functionally overrepresented and found to act as hubs, suggesting that their dysregulation could drive the chronic inflammation seen in both diseases. This shared molecular architecture supports the hypothesis that a subset of ligands could modulate both conditions simultaneously.

CABS-flex simulations added a conformational dimension to the protein dataset, producing ten models per protein and ultimately selecting three distinct conformers per target for downstream analysis. This structural diversity was critical in ensuring that the subsequent docking simulations reflected realistic flexibility in target proteins.

The docking analysis, encompassing 432 conformers and 56 ligands, generated over 240,000 poses. A threshold of -10 kcal/mol was used to retain only high-affinity interactions. Bubble plot visualizations helped identify frequent binders such as Luteolin 7-O-(β -D-glucuronide), Quercetin 3,7-O- β -D-diglucoside, Kaempferol 3,7-O-diglucoside, and Apigenin 7-O-glucuronide—each interacting with a broad panel of proteins. Importantly, ligands that repeatedly targeted shared disease proteins (such as JAK1, IL10RA, IL17A, IL12B) were prioritized for dynamic assessment, based on both binding energy and biological relevance.

MD simulations added temporal resolution to the static docking results and helped assess the stability, compactness, and conformational integrity of the complexes. The following key observations were made:

RMSD profiles demonstrated that ligands such as Luteolin 7-O- β -D-glucuronide, Quercetin 3,7-O- β -D-diglucoside, Kaempferol diglucoside, Apigenin glucuronide, and Myricetin supported protein structural stability, reaching equilibrium within 20–30 ns. Ligand RMSD values for these compounds remained consistently low, confirming that they retained their position within the binding pocket.

SASA analysis showed a mild but consistent downward trend across most complexes, indicating a ligand-induced shielding effect and a tendency of proteins to adopt more compact conformations. This reduction in solvent exposure may correlate with improved protein–ligand compatibility and lower entropic penalties during binding.

Radius of Gyration (Rg) values further validated these findings. Most proteins preserved their compactness throughout the simulation period, with only slight ligand-dependent variations. Complexes like IL17A + 4,5-dicaffeoylquinic acid and IL23R + Luteolin-7-O-acetylglucoside showed slight decreases in Rg, consistent with structural stabilization.

Hydrogen bond analysis provided a quantitative measure of interaction strength and continuity. Ligands such as Luteolin 7-O-(β -D-glucuronide) and Quercetin 3,7-O- β -D-diglucoside formed between 6 to 10 hydrogen bonds on average with multiple targets including IL17A, JAK1, IL10RA, and IFNG. Other ligands such as Kaempferol diglucoside, Apigenin derivatives, and Epicatechin gallate maintained 3–6 hydrogen bonds, demonstrating a sufficient level of interaction to support complex stability.

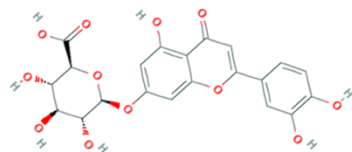
Together, these simulation-based parameters converged on a core set of ligands that not only bound strongly in static docking but also preserved protein architecture and binding conformation under dynamic conditions.

MM/GBSA analysis quantified the thermodynamic favorability of the complexes post-simulation. The most potent interactions were observed with Luteolin-7-O-glucoside ($\Delta G_{\text{total}} = -62.95$ kcal/mol with IL12B), Luteolin 7-O-glucuronide, and Quercetin derivatives, which consistently achieved ΔG values below -50 kcal/mol across several proteins. These data correlate strongly with their RMSD and hydrogen bond stability and reinforce their selection as lead candidates.

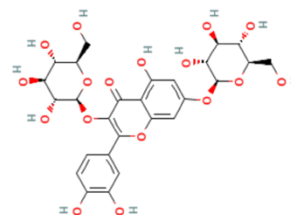
Moreover, ligand occurrence frequency analysis in the final filtered 120 complexes revealed that these same ligands were not only thermodynamically favorable but also recurrent, highlighting their binding versatility and multi-target potential. For instance, Luteolin 7-O-glucuronide appeared in 19 unique complexes, making it the most frequent and robust ligand in the dataset.

Flavonoid derivatives such as Luteolin 7-O-(β -D-glucuronide), Quercetin 3,7-O- β -D-diglucoside, and Apigenin 7-O-glucuronide, which contain glucuronide or diglucoside substitutions, exhibited low energy values in both molecular docking analyses (binding affinity) and MM/GBSA binding free energy (ΔG_{total}) calculations. These ligands demonstrated high binding affinity and strong protein-target interaction properties at both static and dynamic conditions according to the results. The robust binding capability of these compounds stems from their distinctive chemical structures and molecular arrangements. The basic structure of flavonoids, known as the C6–C3–C6 skeleton, includes two aromatic rings and a conjugated π -system, which enables π – π stacking interactions with aromatic amino acid residues within the protein binding pockets (**Figure 5.1**). These molecules contain several hydroxyl groups that specifically in Quercetin 3,7-O- β -D-diglucoside create extensive hydrogen bond interactions with polar amino acids in the binding site (**Harborne & Williams, 2000**). Glucuronide derivatives enhance protein binding by their carboxyl group which interacts through electrostatic forces with positively charged amino acids. The glucuronic acid and glucose units increase hydrophilicity and directionality which enables the ligand to position itself more optimally on the protein surface. The flexible nature of the carbohydrate groups allows the ligand to enter the binding pocket more effectively (**Harborne & Williams, 2000**). These ligands form more hydrogen bonds during simulations while maintaining their binding position during dynamic conditions which helps stabilize the protein structure. The low binding affinity scores obtained from docking simulations calculated the low ΔG_{total} values and validated the thermodynamic stability and biological relevance of these compounds when interacting with target proteins. Flavonoid derivatives that incorporate glucuronide or diglucoside groups exhibit superior binding energy along with stable interactions which confirms their potential as multi-target therapeutic agents.

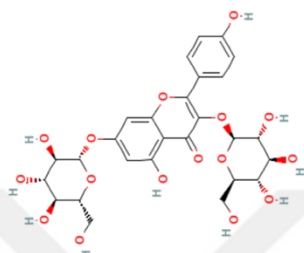
Luteolin 7-O-(β -D-glucuronide)



Quercetin 3,7-O- β -D-diglucoside



Kaempferol-3,7-diglucoside



Quercetin-7-O- β -D glucoside

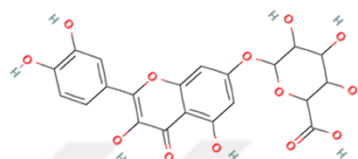


Figure 5.1. Chemical structures of Luteolin 7-O-(β -D-glucuronide), Quercetin 3,7-O- β -D-diglucoside, Apigenin 7-O-glucuronide, and Kaempferol 3,7-O-diglucoside.

6. CONCLUSION

In this thesis study, common and specific protein targets involved in chronic inflammatory skin diseases such as psoriasis and atopic dermatitis (AD) were identified using computational biology approaches, and the therapeutic potential of plant-based phenolic compounds against these targets was evaluated through multi-layered analyses. The protein pool derived from a literature review was expanded using a protein–protein interaction (PPI) network, identifying shared targets between AD and psoriasis, particularly immune response-related proteins such as JAK1, IL17A, IL6, IFNG, and IL23A. This finding demonstrated the existence of common molecular mechanisms among inflammatory skin diseases and opened a new window for multi-targeted treatment strategies.

The structural flexibilities of these common proteins were analyzed using CABS-flex simulations, and then 56 different phenolic compounds were docked to the selected protein conformations. Docking results revealed that certain compounds, particularly Luteolin 7-O-(β -D-glucuronide), Quercetin 3,7-O- β -D-diglucoside, and Kaempferol 3,7-O-diglucoside, exhibit high binding affinity toward multiple target proteins. This suggests that the flavonoids in question may exhibit multi-target effects and modulate different stages of the inflammatory response simultaneously.

Molecular dynamics simulations confirmed that the selected complexes remain stable under dynamic conditions. SASA and Rg analyses demonstrated that ligand binding affects protein compactness, while hydrogen bond analyses revealed the continuity of intra-complex interactions. MM/GBSA binding energy analyses showed that most of these compounds exhibit strong bindings below -50.0 kcal/mol. All these data supported that natural phenolic compounds can target inflammatory pathways in a multifaceted manner and can be evaluated as potential therapeutic agents

This study has laid an important foundation, both theoretically and practically, by offering a holistic treatment approach based on common protein targets, rather than focusing on a single disease. The findings strongly supported the potential use of natural compounds as multi-target anti-inflammatory agents and suggested that common treatment strategies may be possible for immune-based diseases such as AD and psoriasis.

In future studies, it is of great importance to experimentally validate the biological validity of the ligand-protein complexes identified in this thesis. It is necessary to evaluate the effects of these compounds on target protein expression and inflammatory markers in cell culture models, test their cytotoxicity, determine dose-response relationships, and elucidate their effects on intracellular signaling pathways. Additionally, in silico analysis of ADME/Tox profiles, development of suitable formulations, and studies to enhance bioavailability using carrier systems such as nanoparticles or liposomes should also be conducted.

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BIOGRAPHY

Sinem Nur YAYLA commenced her undergraduate studies in 2017 at Istanbul Arel University, majoring in Molecular Biology and Genetics. She later pursued her master's degree in the Department of Biotechnology at the Graduate School of Gebze Technical University, where she actively contributed to several national and international research projects in the fields of computational biology, genetic variant analysis, and in silico drug discovery.



PUBLICATIONS AND PRESENTATIONS FROM THE THESIS

Yayla, S. N., & Özbil, M. (2025, March 8–9). *Discovery of plant-based phenolic compounds to fight against psoriasis and atopic dermatitis* [Oral presentation]. 3rd International Üsküdar Scientific Research Congress, Istanbul, Türkiye. ISARC – International Science Research Center.



APPENDICES

APPENDIX-A. Flavonoid Compounds

Table A-1 Flavonoid Compounds and Their Association with marianum, Taraxacum officinale, and Brassica nigra

Phenolic Compounds	Silybum marianum	Taraxacum officinale	Brassica nigra
3,5-Dicaffeoylquinic acid	✓	✓	✓
3,4-Dicaffeoylquinic acid	✓	✓	✓
3,4,7-Trimethoxyquercetin	✓	✓	✓
4-O-Caffeoylquinic acid	✓	✓	✓
4,5-Dicaffeoylquinic acid	✓	✓	✓
5-O-Dicaffeoylquinic acid	✓	✓	✓
5-p-Coumaroylquinic acid	✓	✓	✓
Aesculin	✓	✓	✓
Apigenin	✓	✓	✓
Apigenin 7-O-glucuronide	✓	✓	
Apigenin O-glucoside	✓	✓	✓
Artemetin	✓	✓	✓
Caffeic acid	✓	✓	✓

Table A-1 Continue

Caffeic acid	✓	✓	✓
Catechin	✓	✓	✓
Chlorogenic acid	✓	✓	✓
Chrysin	✓	✓	✓
Chrysoeriol	✓	✓	
Cichorin	✓		
Cichoric acid	✓	✓	✓
Cynarin	✓	✓	
Ellagic acid	✓	✓	✓
Epicatechin	✓	✓	✓
Epicatechin gallate	✓	✓	✓
Esculetin		✓	
Ferulic acid	✓	✓	✓
Gallic acid		✓	✓
Genkwanin	✓	✓	✓
Hesperitin	✓	✓	✓

Table A-1 Continue

Isoetin	✓	✓	✓
Isoferulic acid	✓	✓	✓
Isovitexin		✓	
Kaempferol	✓	✓	✓
Kaempferol 3,7-O-diglucoside	✓	✓	✓
Kaempferol 3-O-β-D-glucoside	✓	✓	✓
Kaempferol 3-O-rhamnoside	✓	✓	✓
Luteolin	✓	✓	✓
Luteolin 7-O-acetylglucoside	✓	✓	✓
Luteolin 7-O-β-D-glucoside	✓	✓	✓
Luteolin 7-O-β-D-glucuronide	✓	✓	
Myricetin	✓	✓	✓
Naringenin	✓	✓	✓
Nortrachelogenin C-β-D-glucoside	✓	✓	✓
p-Coumaric acid	✓	✓	✓
Protocatechuic acid	✓	✓	✓

Table A-1 Continue

Luteolin 7-O-(β -D-glucuronide)		✓	
Quercetin	✓	✓	✓
Quercetin 3,7-O- β -D-diglucoside		✓	✓
Quercetin 7-O- β -D-glucoside		✓	✓
Rosmarinic acid	✓	✓	✓
Syringic acid			✓
Scopoletin	✓	✓	✓
Silibinin	✓		✓
trans-3,5-O-dicaffeoylquinic acid	✓	✓	✓
Umbelliferone	✓	✓	✓
Vanillic acid			✓
4-Hydroxybenzoic acid	✓	✓	✓

APPENDIX-B. Molecular Docking Results

Table B-1. Binding Affinities of Phenolic Ligands with Target Proteins

Ligand	Protein	Conformer	Binding Affinity
Luteolin 7-O-(β -D-glucuronide)	JAK1	Model 8	-10.7
Quercetin 7-O- β -D-glucoside	JAK1	Model 8	-10.3
Quercetin 3,7-O- β -D-diglucoside	JAK1	Model 8	-10.4
3,5-Dicaffeoylquinic acid	JAK1	Model 8	-10.1
Epicatechin gallate	JAK1	Model 8	-10.1
trans-3,5-O-dicaffeoylquinic acid	JAK1	Model 8	-10.1
Kaempferol 3,7-O-diglucoside	JAK1	Model 8	-10.1
Luteolin 7-O-(β -D-glucuronide)	JAK1 Dimeric	Model 5	-12.7
Quercetin 7-O- β -D-glucoside	JAK1 Dimeric	Model 5	-11.1
Kaempferol 3,7-O-diglucoside	JAK1 Dimeric	Model 5	-10.9
Luteolin 7-O-acetylglucoside	JAK1 Dimeric	Model 5	-10.8
Luteolin 7-O- β -D-glucoside	JAK1 Dimeric	Model 5	-10.8
Apigenin 7-O-glucuronide	JAK1 Dimeric	Model 5	-10.3

Table B-1 Continue

3,5-Dicaffeoylquinic acid	JAK1 Dimeric	Model 5	-10.1
Apigenin O-glucoside	JAK1 Dimeric	Model 5	-10.1
Epicatechin gallate	JAK1 Dimeric	Model 5	10.0
Luteolin 7-O-(β -D-glucuronide)	IFNGR1 Complex	Model 5	-11.9
Quercetin 3,7-O- β -D-diglucoside	IFNGR1 Complex	Model 5	-11.5
Kaempferol 3,7-O-diglucoside	IFNGR1 Complex	Model 5	-11.0
Luteolin 7-O- β -D-glucoside	IFNGR1 Complex	Model 5	-10.8
Isoetin	IFNGR1 Complex	Model 5	-10.7
Apigenin 7-O-glucuronide	IFNGR1 Complex	Model 5	-10.3
Luteolin 7-O-acetylglucoside	IFNGR1 Complex	Model 5	-10.1
Luteolin 7-O-(β -D-glucuronide)	IFNG Complex	Model 1	-13.2
Quercetin 3,7-O- β -D-diglucoside	IFNG Complex	Model 1	-11.9
Kaempferol 3,7-O-diglucoside	IFNG Complex	Model 1	-10.9
trans-3,5-O-dicaffeoylquinic acid	IFNG Complex	Model 1	-10.7

Table B-1 Continue

Epicatechin gallate	IFNG Complex	Model 1	-10.4
Apigenin 7-O-glucuronide	IFNG Complex	Model 1	-10.3
Quercetin 7-O- β -D-glucoside	IFNG Complex	Model 1	-10.2
4,5-Dicaffeoylquinic acid	IFNG Complex	Model 1	-10.1
Luteolin 7-O- β -D-glucoside	IFNG Complex	Model 1	-10.0
Luteolin 7-O-(β -D-glucuronide)	IFNG Complex	Model 1	-13.2
Quercetin 3,7-O- β -D-diglucoside	IFNG Complex	Model 1	-11.9
Kaempferol 3,7-O-diglucoside	IFNG Complex	Model 1	-10.9
trans-3,5-O-dicaffeoylquinic acid	IFNG Complex	Model 1	-10.7
Epicatechin gallate	IFNG Complex	Model 1	-10.4
Apigenin 7-O-glucuronide	IFNG Complex	Model 1	-10.3
Quercetin 7-O- β -D-glucoside	IFNG Complex	Model 1	-10.2
4,5-Dicaffeoylquinic acid	IFNG Complex	Model 1	-10.1

Table B-1 Continue

Luteolin 7-O- β -D-glucoside	IFNG Complex	Model 1	-10.0
Quercetin 7-O- β -D-glucoside	IL10RA	Model 8	-11.3
Apigenin O-glucoside	IL10RA	Model 8	-11.0
Apigenin 7-O-glucuronide	IL10RA	Model 8	-10.9
Luteolin 7-O-acetylglucoside	IL10RA	Model 8	-10.9
Luteolin 7-O- β -D-glucoside	IL10RA	Model 8	-10.9
Apigenin O-glucoside	IL10RA	Model 8	-10.9
Luteolin 7-O-(β -D-glucuronide)	IL10RA	Model 8	-10.8
3,5-Dicaffeoylquinic acid	IL10RA	Model 8	-10.7
Nortrachelogenin C- β -D-glucoside	IL10RA	Model 8	-10.6
Quercetin 3,7-O- β -D-diglucoside	IL10RA	Model 8	-10.6
Kaempferol 3-O- β -D-glucoside	IL10RA	Model 8	-10.6
Luteolin 7-O-(β -D-glucuronide)	IL12B	Model 4	-11.7
Quercetin 3,7-O- β -D-diglucoside	IL12B	Model 4	-10.2
Kaempferol 3,7-O-diglucoside	IL12B	Model 4	-10.1
Apigenin 7-O-glucuronide	IL12B	Model 4	-9.8
Quercetin 7-O- β -D-glucoside	IL12B	Model 4	-9.8
Luteolin	IL12RB1	Model 6	-10.8

Table B-1 Continue

Kaempferol 3,7-O-diglucoside	IL12RB1	Model 6	-10.2
Quercetin 3,7-O- β -D-diglucoside	IL12RB1	Model 6	-10.0
Luteolin 7-O-(β -D-glucuronide)	IL17A Complex	Model 3	-12.1
Quercetin 3,7-O- β -D-diglucoside	IL17A Complex	Model 3	-11.9
Kaempferol 3,7-O-diglucoside	IL17A Complex	Model 3	-11.5
Quercetin 7-O- β -D-glucoside	IL17A Complex	Model 3	-10.8
trans-3,5-O-dicaffeoylquinic acid	IL17A Complex	Model 3	-10.8
3,5-Dicaffeoylquinic acid	IL17A Complex	Model 3	-10.3
Isovitexin	IL17A Complex	Model 3	-10.7
Luteolin 7-O- β -D-glucoside	IL17A Complex	Model 3	-10.6
Apigenin 7-O-glucuronide	IL17A Complex	Model 3	-10.5
4,5-Dicaffeoylquinic acid	IL17A Complex	Model 3	-10.2
Isoetin	IL17A Complex	Model 3	-10.4
Luteolin 7-O-acetylglucoside	IL17A Complex	Model 3	-10.4

Table B-1 Continue

Luteolin 7-O-(β -D-glucuronide)	IL17RC	Model 6	-11.1
Quercetin 3,7-O- β -D-diglucoside	IL17RC	Model 6	-10.3
Luteolin 7-O- β -D-glucoside	IL17RC	Model 6	-10.2
Quercetin 7-O- β -D-glucoside	IL17RC	Model 6	-10.1
Luteolin 7-O-(β -D-glucuronide)	IL23A	Model 2	-13.1
Apigenin O-glucoside	IL23A	Model 2	-11.9
Silybin	IL23A	Model 2	-11.9
Apigenin 7-O-glucuronide	IL23A	Model 2	-11.7
Quercetin 7-O- β -D-glucoside	IL23A	Model 2	-11.6
Epicatechin gallate	IL23A	Model 2	-11.3
3,5-Dicaffeoylquinic acid	IL23A	Model 2	-11.2
Kaempferol 3,7-O-diglucoside	IL23A	Model 2	-10.8
Isovitexin	IL23A	Model 2	-10.7
Myricetin	IL23A	Model 2	-10.6
trans-3,5-O-dicaffeoylquinic acid	IL23A	Model 2	-10.4
Quercetin	IL23A	Model 2	-10.4
Luteolin 7-O-(β -D-glucuronide)	IL23R	Model 3	-11.8
Quercetin 3,7-O- β -D-diglucoside	IL23R	Model 3	-10.7
Apigenin 7-O-glucuronide	IL23R	Model 3	-10.3

Table B-1 Continue

Luteolin 7-O-acetylglucoside	IL23R	Model 3	-10.2
Kaempferol 3,7-O-diglucoside	IL23R	Model 3	-10.1
Luteolin 7-O-(β -D-glucuronide)	JAK2	Model 5	-11.9
Quercetin 3,7-O- β -D-diglucoside	JAK2	Model 5	-11.6
Kaempferol 3,7-O-diglucoside	JAK2	Model 5	-10.6
Quercetin 7-O- β -D-glucoside	JAK2	Model 5	-9.9
trans-3,5-O-dicaffeoylquinic acid	JAK2	Model 5	-9.8
3,5-Dicaffeoylquinic acid	JAK2	Model 5	-9.9
Isovitexin	JAK2	Model 5	-10.2
Luteolin 7-O- β -D-glucoside	JAK2	Model 5	-9.9
Apigenin 7-O-glucuronide	JAK2	Model 5	-9.8
4,5-Dicaffeoylquinic acid	JAK2	Model 5	-10.0
Luteolin 7-O-(β -D-glucuronide)	IFNG	Model 8	-11.8
Quercetin 3,7-O- β -D-diglucoside	IFNG	Model 8	-11.4
Kaempferol 3,7-O-diglucoside	IFNG	Model 8	-11.1
3,5-Dicaffeoylquinic acid	IFNG	Model 8	-10.6
Aesculin	IFNG	Model 8	-10.1
Cichoric acid	IFNG	Model 8	-10.0
Apigenin 7-O-glucuronide	IFNG	Model 8	-10.0

Table B-1 Continue

Luteolin 7-O-(β -D-glucuronide)	IFNGR1	Model 6	-11.0
Luteolin 7-O-(β -D-glucuronide)	IL1B	Model 6	-11.6
3,5-Dicaffeoylquinic acid	IL1B	Model 5	-9.9
Luteolin 7-O-(β -D-glucuronide)	IL6 Complex	Model 1	-10.4
Quercetin 7-O- β -D-glucoside	IL6 Complex	Model 1	-9.8
Luteolin 7-O-(β -D-glucuronide)	IL17A	Model 8	-10.9
Epicatechin gallate	IL17A	Model 8	-10.4
Quercetin 3,7-O- β -D-diglucoside	IL17A	Model 8	-10.0
4,5-Dicaffeoylquinic acid	IL17A	Model 8	-9.8
Luteolin 7-O-(β -D-glucuronide)	IL23R	Model 4	-10.5
Kaempferol 3,7-O-diglucoside	IL23R	Model 4	-9.9
Luteolin 7-O-(β -D-glucuronide)	TNF	Model 6	-11.3
Chrysin	TNF	Model 6	-10.6
Apigenin	TNF	Model 6	-10.1
Naringenin	TNF	Model 6	-10.0
Quercetin	TNF	Model 6	-9.9
Luteolin 7-O-(β -D-glucuronide)	IL6 Complex	Model 7	-11.7

Table B-1 Continue

Quercetin 3,7-O- β -D-diglucoside	IL6 Complex	Model 7	-10.7
Kaempferol 3,7-O-diglucoside	IL6 Complex	Model 7	-10.5
Quercetin 7-O- β -D-glucoside	IL6 Complex	Model 7	-10.2
Epicatechin gallate	IL6 Complex	Model 7	-10.1
Silybin	IL6 Complex	Model 7	-10.1
Isoetin	IL6 Complex	Model 7	-10.4
Kaempferol 3-O- β -D-glucoside	IL6 Complex	Model 7	-10.0

APPENDIX-C. Hydrogen Bond Analysis

Table C-1. Average Number of Hydrogen Bonds Between Selected Phenolic Ligands and Target Proteins During Molecular Dynamics Simulations

Protein	Ligand	Average Hbond number
IFNG Complex	Luteolin 7-O-(β -D-glucuronide)	9.89
IL17A Complex	Quercetin 3,7-O- β -D-diglucoside	7.42
JAK1 Dimeric	Luteolin 7-O-(β -D-glucuronide)	7.4
IFGMR1 Complex	Quercetin 3,7-O- β -D-diglucoside	6.83
IL17A Complex	Luteolin 7-O-(β -D-glucuronide)	6.42

Table C-1 Continue

IFNG Complex	Luteolin 7-O-(β -D-glucuronide)	9.89
IL17A Complex	Quercetin 3,7-O- β -D-diglucoside	7.42
JAK1	Quercetin 3,7-O- β -D-diglucoside	6.41
IL12B	Luteolin 7-O-(β -D-glucuronide)	6.28
IL12B	Kaempferol 3,7-O-diglucoside	5.91
IL12B	Quercetin 3,7-O- β -D-diglucoside	5.83
IL10RA	Luteolin 7-O-(β -D-glucuronide)	5.66
IL6 Complex	Kaempferol 3,7-O-diglucoside	5.56
IFNG Complex	Quercetin 3,7-O- β -D-diglucoside	5.43
IFGNR1 Complex	Luteolin 7-O- β -D-glucoside	5.41
IL23R	Luteolin 7-O-(β -D-glucuronide)	5.35
IFGNR1 Complex	Kaempferol 3,7-O-diglucoside	5.34
IFNG Complex	Quercetin 3,7-O- β -D-diglucoside	5.19
IL17A Complex	Quercetin 7-O- β -D-glucoside	5.15
IFGNR1 Complex	Apigenin 7-O-glucuronide	5.12
IL17RC	Quercetin 7-O- β -D-glucoside	5.12
IL1B	Luteolin 7-O-(β -D-glucuronide)	5.00
IFGNR1 Complex	Aesculin	4.96
JAK2	Luteolin 7-O-(β -D-glucuronide)	4.90
IL10RA	3,4-Dicaffeoylquinic acid	4.72
IL10RA	Quercetin 3,7-O- β -D-diglucoside	4.7
IFNG Complex	Kaempferol 3,7-O-diglucoside	4.67
IL23A	Quercetin 7-O- β -D-glucoside	4.61
JAK2	Apigenin 7-O-glucuronide	4.52

Table C-1 Continue

IL6	Luteolin 7-O-(β -D-glucuronide)	4.48
JAK1 Dimeric	Epicatechin gallate	4.37
IL6 Complex	Quercetin 3,7-O- β -D-diglucoside	4.31
IL10RA	Kaempferol 3,7-O-diglucoside	4.29
IL17A Complex	4,5-Dicaffeoylquinic acid	4.26
IL6 Complex	Luteolin 7-O-(β -D-glucuronide)	4.23
IL23R	Apigenin 7-O-glucuronide	4.21
IL10RA	Nortrachelogenin C- β -D-glucoside	4.14
JAK1 Dimeric	Kaempferol 3,7-O-diglucoside	4.13
IL17A Complex	Kaempferol 3,7-O-diglucoside	4.03
IL12RBI	Luteolin 7-O-(β -D-glucuronide)	4.02
IL17A	Epicatechin gallate	3.99
IL23A	Luteolin 7-O- β -D-glucoside	3.97
JAK1	Kaempferol	3.9
IL23R	Kaempferol 3,7-O-diglucoside	3.89
IL17A	Luteolin 7-O-(β -D-glucuronide)	3.87
JAK2	Quercetin 3,7-O- β -D-diglucoside	3.84
IL23R	Quercetin 3,7-O- β -D-diglucoside	3.8
JAK1	Apigenin 7-O-glucuronide	3.72
JAK1	3,5-Dicaffeoylquinic acid	3.71
IL17A	Quercetin 3,7-O- β -D-diglucoside	3.69
IL10RA	Kaempferol 3-O- β -D-glucoside	3.67
IL10RA	Isovitexin	3.65

Table C-1 Continue

JAK1	Quercetin 7-O- β -D-glucoside	3.65
IFNG	Luteolin 7-O-(β -D-glucuronide)	3.63
JAK2	Myricetin	3.6
IL12B	Apigenin 7-O-glucuronide	3.57
JAK2	Quercetin 7-O- β -D-glucoside	3.56
JAK1	Luteolin 7-O-(β -D-glucuronide)	3.56
IL23A	Epicatechin gallate	3.55
JAK1	Apigenin O-glucoside	3.47
IL10RA	3,5-Dicaffeoylquinic acid	3.43
IL23R	Luteolin 7-O-acetylglucoside	3.41
SIFNG	3,5-Dicaffeoylquinic acid	3.38
IFNG Complex	Epicatechin gallate	3.34
IL1B	3,5-Dicaffeoylquinic acid	3.31
IL23A	Isovitexin	3.31
JAK1 Dimeric	3,5-Dicaffeoylquinic acid	3.31
IL23A	Myricetin	3.29
IL12RBI	Kaempferol 3,7-O-diglucoside	3.18
IL17A Complex	Apigenin 7-O-glucuronide	3.16
IL23A	trans-3,5-O-dicaffeoylquinic acid	3.12
IL17A Complex	Isovitexin	3.08
JAK2	Luteolin 7-O-acetylglucoside	3.03
IFNG	Cichoric acid	2.99
IFGNR1 Complex	Hesperetin	2.98
IFNG	Aesculin	2.97

Table C-1 Continue

IL10RA	Apigenin 7-O-glucuronide	2.87
IFNG	Apigenin 7-O-glucuronide	2.83
IL23A	Quercetin 3,7-O- β -D-diglucoside	2.78
IL12B	Quercetin 7-O- β -D-glucoside	2.76
IL10RA	Epicatechin gallate	2.74
IL23A	Cichoric acid	2.7
IL23A	Apigenin O-glucoside	2.65
IL23A	Kaempferol 3,7-O-diglucoside	2.61
IL10RA	Apigenin O-glucoside	2.56
JAK1	Luteolin 7-O- β -D-glucoside	2.55
JAK2	Kaempferol 3,7-O-diglucoside	2.55
IFGNR1	Isovitexin	2.55
IL6	Quercetin 7-O- β -D-glucoside	2.47
IFNG Complex	trans-3,5-O-dicaffeoylquinic acid	2.47
IL17RC	Luteolin 7-O-(β -D-glucuronide)	2.46
IL1B	Silibinin	2.45
IL23A	Apigenin 7-O-glucuronide	2.4
IFGNR1 Complex	Isoetin	2.38
IL10RA	Quercetin 7-O- β -D-glucoside	2.35
IL10RA	Luteolin 7-O- β -D-glucoside	2.31
IL23A	4,5-Dicaffeoylquinic acid	2.29
IL23A	3,5-Dicaffeoylquinic acid	2.28
IL17RC	Luteolin 7-O- β -D-glucoside	2.17
JAK1 Dimeric	Quercetin 7-O- β -D-glucoside	2.17

Table C-1 Continue

IFGNR1 Complex	Myricetin	2.17
IFGNR1 Complex	Luteolin	2.13
IL17RC	Quercetin 3,7-O- β -D-diglucoside	2.11
IL10RA	Luteolin 7-O-acetylglucoside	2.06
IL23A	Kaempferol 3-O- β -D-glucoside	2.04
JAK1 Dimeric	trans-3,5-O-dicaffeoylquinic acid	2.02
IFGNR1 Complex	Ellagic acid	1.8
IL17A Complex	Luteolin 7-O- β -D-glucoside	1.7
TNF	Naringenin	1.68
IL6 Complex	Isoetin	1.67
IFNG	Epicatechin gallate	1.65
IFGNR1 Complex	Luteolin 7-O-acetylglucoside	1.63
IFGNR1 Complex	Quercetin	1.36

APPENDIX-D. Binding Energy Analysis

Table D-1 Average ΔG_{total} Binding Energies of Ligand–Protein Complexes

Protein	Ligand	Average ΔG_{total}
IL12B	Luteolin-7-O-glucoside	-62.95
IL10RA	Luteolin 7-O-(β -D-glucuronide)	-61.64
IL10RA	3-4-Di-caffeoylquinicacid	-61.02
IL23R	Luteolin-7-O-glucoside	-59.09
IL10RA	Kaempferol-3-O- β -D-glucoside	-57.18
IL10RA	Kaempferol-3,7-diglucoside	-57.0
JAK1 Dimeric	Epicatechin gallate	-55.92

Table D-1 Continue

JAK1 Dimeric	Luteolin-7-O-glucoside	-54.01
JAK2	Luteolin 7-O- β -D-glucoside	-54.01
IL23A	Apigenin 7-O-glucuronide	-52.57
JAK2	Luteolin 7-O-(β -D-glucuronide)	-52.21
IL6	Luteolin-7-O-glucoside	-51.79
IL17A Complex	Luteolin-7-O-glucoside	-51.27
IL17A Complex	Quercetin 3,7-O- β -D-diglucoside	-50.2
IL10RA	Quercetin 3,7-O- β -D-diglucoside	-49.7
IL12B	Quercetin 3,7-O- β -D-diglucoside	-49.6
IL17A Complex	Quercetin-7-O- β -D-glucoside	-49.4
JAK1 Dimeric	Quercetin-7-O- β -D-glucoside	-49.16
JAK1	Quercetin 3,7-O- β -D-diglucoside	-48.88
IFGMR1 Complex	Luteolin 7-O- β -D-glucoside	-48.8
IL12B	Kaempferol-3,7-diglucoside	-47.83
IFNG	Quercetin 3,7-O- β -D-diglucoside	-47.22
TNF	Luteolin-7-O-glucoside	-46.64
IFNG	Luteolin-7-O-glucoside	-46.44
JAK1	Kaempferol	-45.66
IFNG Complex	Luteolin 7-O- β -D-glucoside	-44.68
IL6 Complex	Luteolin-7-O-glucoside	-43.45
IL17RC	Quercetin-7-O- β -D-glucoside	-42.79
IL10RA	Luteolin-7-O-acetylglucoside	-42.77
JAK2	Apigenin 7-O-glucuronide	-42.15
IL17RC	Luteolin 7-O-(β -D-glucuronide)	-41.82

Table D-1 Continue

IL10RA	Apigenin 7-O-glucoside	-41.58
IFGNR1 Complex	Quercetin 3,7-O- β -D-diglucoside	-41.2
JAK1	Apigenin 7-O-glucuronide	-41.04
IFGNR1 Complex	Kaempferol-3,7-diglucoside	-40.86
IL17A	Epicatechin gallate	-40.59
IFGNR1 Complex	Aesculin	-40.58
JAK2	Quercetin 3,7-O- β -D-diglucoside	-40.35
IL10RA	Nortrachelogenin-C-B-glucoside	-39.6
IL17A	Quercetin 3,7-O- β -D-diglucoside	-39.29
IFNG	Cichoric acid	-38.64
IFNG Complex	Luteolin-7-O-glucoside	-38.56
IL17A	Luteolin-7-O-glucoside	-38.52
IL23A	Isovitexin	-38.51
JAK2	Quercetin-7-O- β -D-glucoside	-38.33
IL10RA	Isovitexin	-37.94
IFNG	3,5-Dicaffeoylquinic acid	-37.88
JAK1 Dimeric	Luteolin 7-O-(β -D-glucuronide)	-37.44
TNF	Apigenin	-37.19
IL23A	Quercetin 3,7-O- β -D-diglucoside	-37.11
JAK1	Luteolin 7-O- β -D-glucoside	-37.09
JAK1 Dimeric	3,5-Dicaffeoylquinic acid	-37.06
JAK2	Myricetin	-36.8
IFGNR1 Complex	Hesperetin	-36.56
JAK1	3,5-Dicaffeoylquinic acid	-36.45

Table D-1 Continue

IL17A Complex	4,5-Dicaffeoylquinic acid	-36.31
TNF	Quercetin	-36.13
IL10RA	Apigenin 7-O-glucuronide	-35.85
IL17A Complex	Luteolin 7-O-(β -D-glucuronide)	-35.57
IL10RA	3,5-Dicaffeoylquinic acid	-35.56
IL23R	Luteolin-7-O-acetylglucoside	-35.45
JAK1	Luteolin 7-O-(β -D-glucuronide)	-35.12
IL1B	Silibinin	-34.92
IL23A	Apigenin 7-O-glucoside	-34.85
IL10RA	Quercetin-7-O- β -D-glucoside	-34.77
IL17A Complex	Apigenin 7-O-glucuronide	-34.57
IL17A Complex	Luteolin 7-O- β -D-glucoside	-34.46
JAK2	Kaempferol-3,7-diglucoside	-34.45
IL6	Luteolin 7-O-(β -D-glucuronide)	-34.37
JAK1	Quercetin-7-B-D	-34.23
JAK1	Apigenin 7-O-glucoside	-33.37
IL12B	Apigenin 7-O-glucuronide	-33.32
TNF	Naringenin	-32.06
IL6 Complex	Luteolin 7-O- β -D-glucoside	-31.84
IL23R	Kaempferol-3,7-diglucoside	-31.79
IFGNR1 Complex	Luteolin-7-O-acetylglucoside	-31.47
IL23A	Myricetin	-31.1
TNF	Chrysin	-31.09
IL6 Complex	Kaempferol-3,7-diglucoside	-31.01

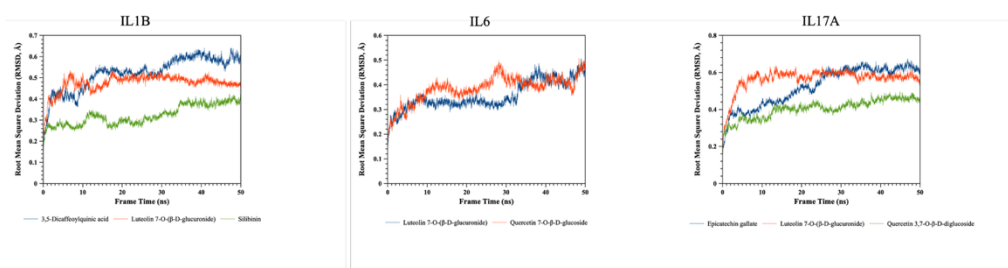
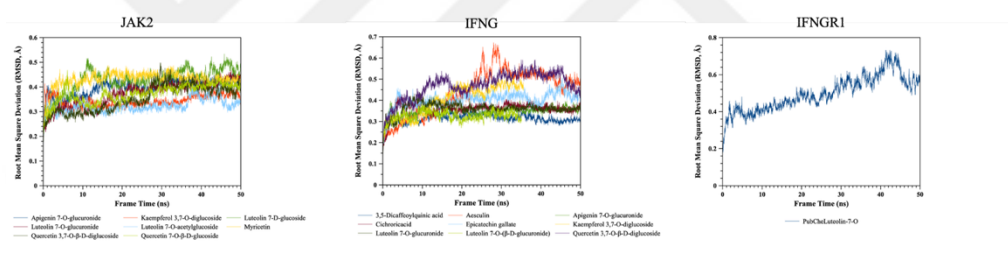
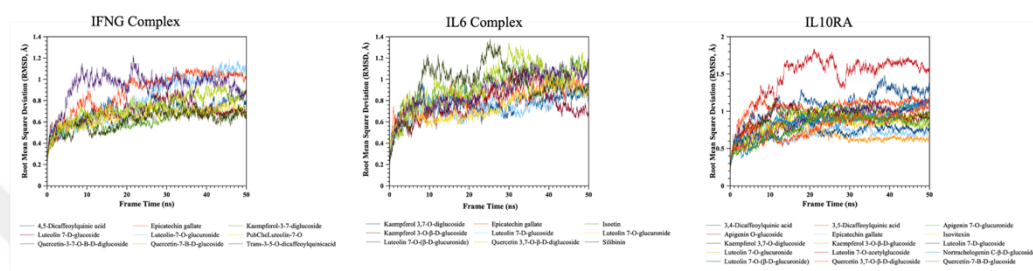
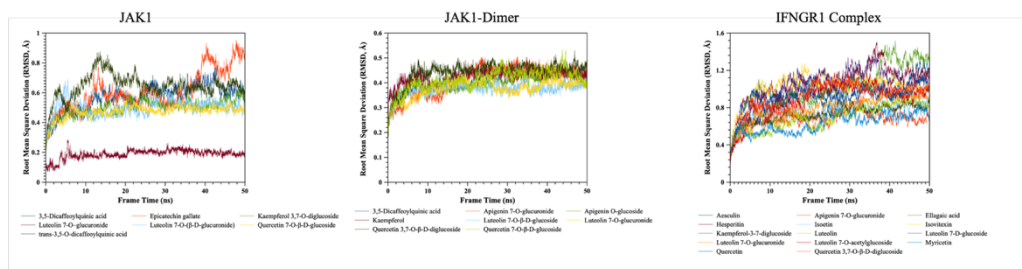
Table D-1 Continue

IL23A	4,5-Dicaffeoylquinic acid	-30.89
IL12B	Quercetin-7-O- β -D-glucoside	-30.63
JAK1 Dimeric	Kaempferol-3,7-diglucoside	-30.47
IFGNR1 Complex	Apigenin 7-O-glucuronide	-30.4
IL17A Complex	Isovitexin	-30.36
IFGNR1 Complex	Myricetin	-30.21
IL23A	Quercetin-7-O- β -D-glucoside	-30.19
IFNG	Aesculin	-30.18
IL10RA	Epicatechin gallate	-29.96
IFNG Complex	Quercetin 3,7-O- β -D-diglucoside	-29.77
JAK1 Dimeric	Trans 3-5-O	-29.72
IFGNR1 Complex	Luteolin 7-O-(β -D-glucuronide)	-29.26
IL12RBI	Kaempferol-3,7-diglucoside	-28.2
IFNGR1	Luteolin-7-O-glucoside	-28.08
IL1B	PubCheLuteolin 7-O	-27.89
IFGNR1 Complex	Luteolin	-27.81
IL6 Complex	Isoetin	-27.65
IL23R	Apigenin 7-O-glucuronide	-26.72
IL17RC	Quercetin 3,7-O- β -D-diglucoside	-26.15
IL17A Complex	Kaempferol-3,7-diglucoside	-26.04
IL23A	Luteolin 7-O-(β -D-glucuronide)	-26.04
IFNG	Kaempferol-3,7-diglucoside	-25.88
IFGNR1 Complex	Ellagic acid	-25.79
IL1B	3,5-Dicaffeoylquinic acid	-25.52

Table D-1 Continue

IFNG	Apigenin 7-O-glucuronide	-25.5
IFGNR1 Complex	Isovitexin	-24.87
IL23R	Quercetin 3,7-O- β -D-diglucoside	-24.47
IL12RBI	Luteolin-7-O-glucoside	-23.99
IL6 Complex	Kaempferol-3-O- β -D-glucoside	-23.55
IL10RA	Luteolin 7-O- β -D-glucoside	-23.26
IFNG Complex	Quercetin-7-O- β -D-glucoside	-23.1
IFNG	Epicatechin gallate	-22.26
IL6 Complex	Quercetin 3,7-O- β -D-diglucoside	-21.67
IL23A	Kaempferol-3-O- β -D-glucoside	-21.52
IFNG	Luteolin 7-O-(β -D-glucuronide)	-21.48
IL17RC	Luteolin 7-O- β -D-glucoside	-20.43
IFGNR1 Complex	Isoetin	-20.33
IL23A	Cichoric acid	-20.3
IFGNR1 Complex	Quercetin	-19.6
IL12B	Luteolin 7-O-(β -D-glucuronide)	-19.27
IL23A	Luteolin-7-O-glucoside	-18.94
IL23A	Kaempferol-3,7-diglucoside	-18.37
IL6	Quercetin-7-O- β -D-glucoside	-18.36
IL6 Complex	Silibinin	-18.24
IFNG Complex	Trans-3,5-O-dicaffeoylquinic acid	-16.75
IL23R	Luteolin 7-O-(β -D-glucuronide)	-15.84
IL6 Complex	Epicatechin gallate	-7.95

APPENDIX-E. Protein RMSD Analysis



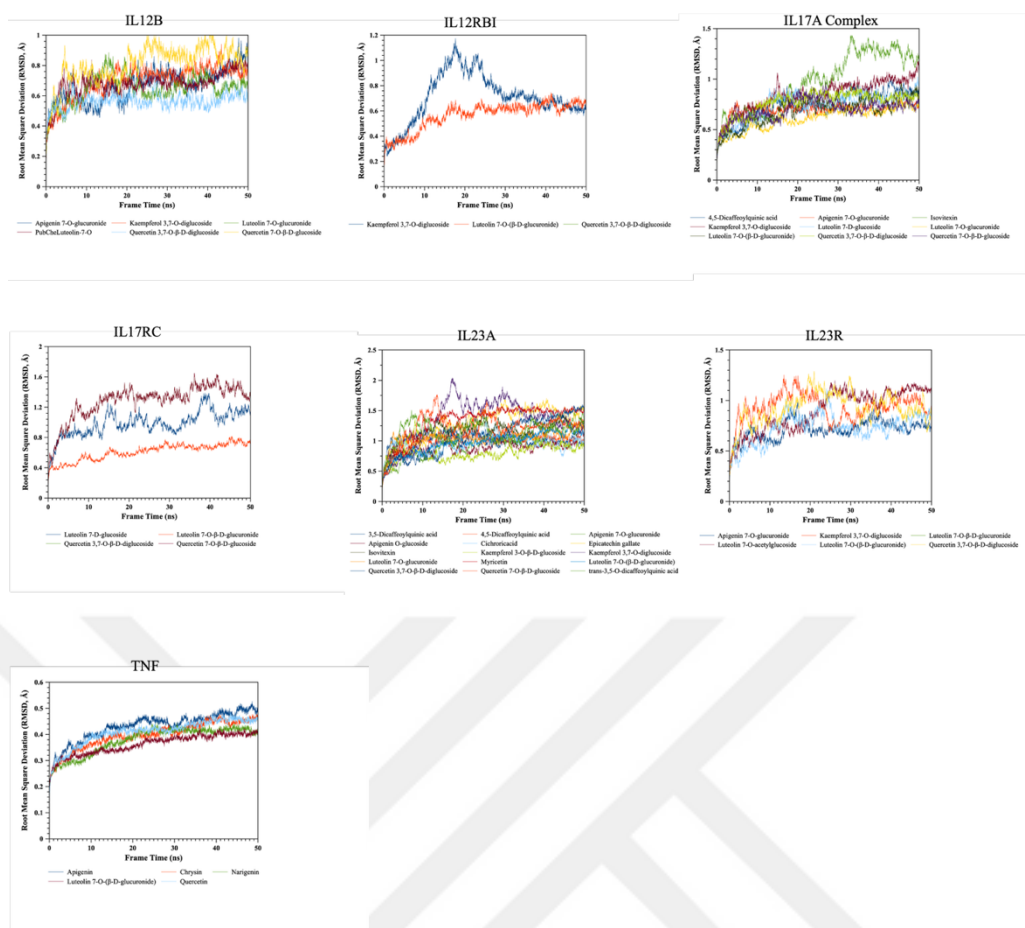
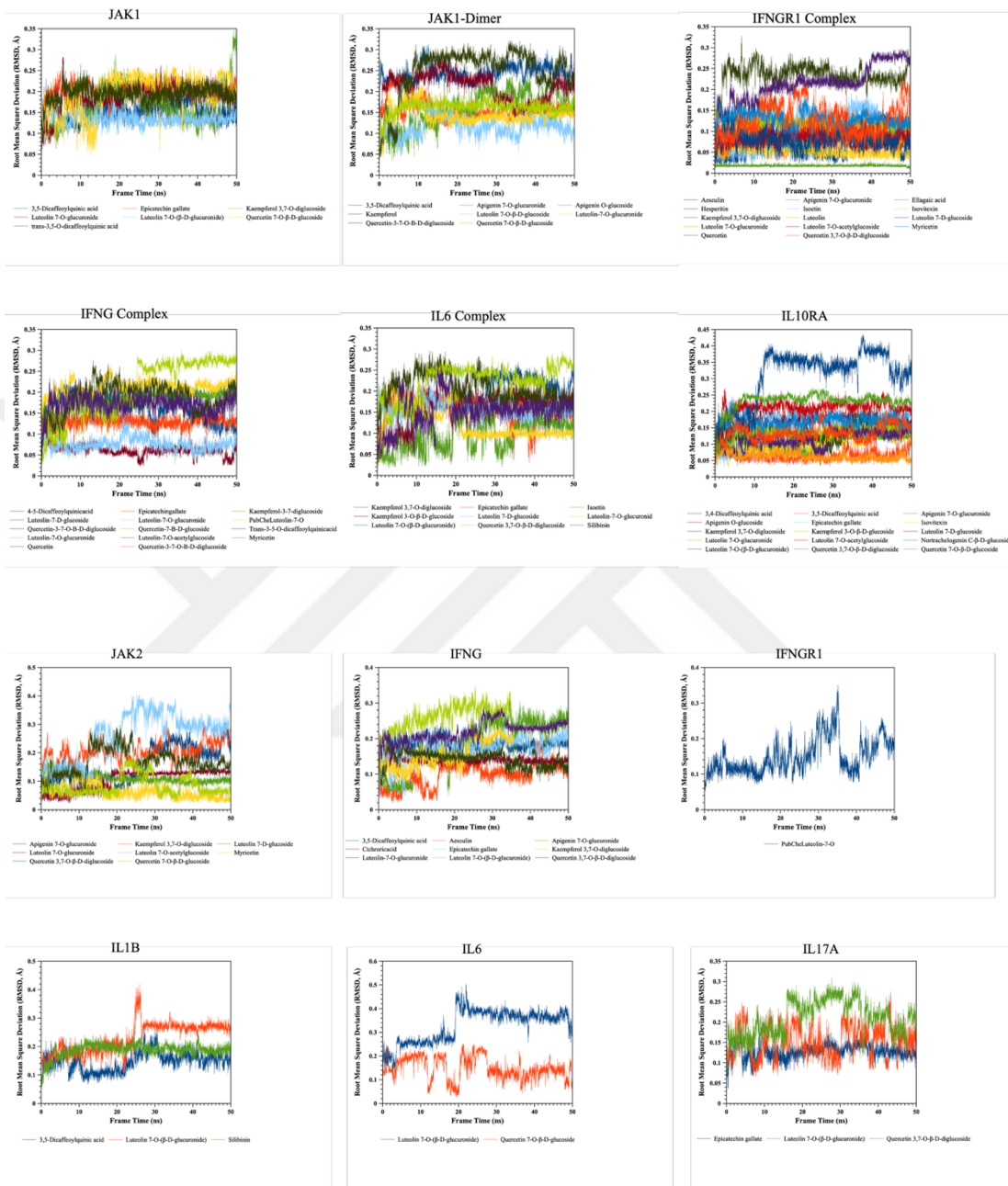


Figure E-1. RMSD Graphs of Protein Structures During Molecular Dynamics Simulations

APPENDIX-F. Ligand RMSD Analysis



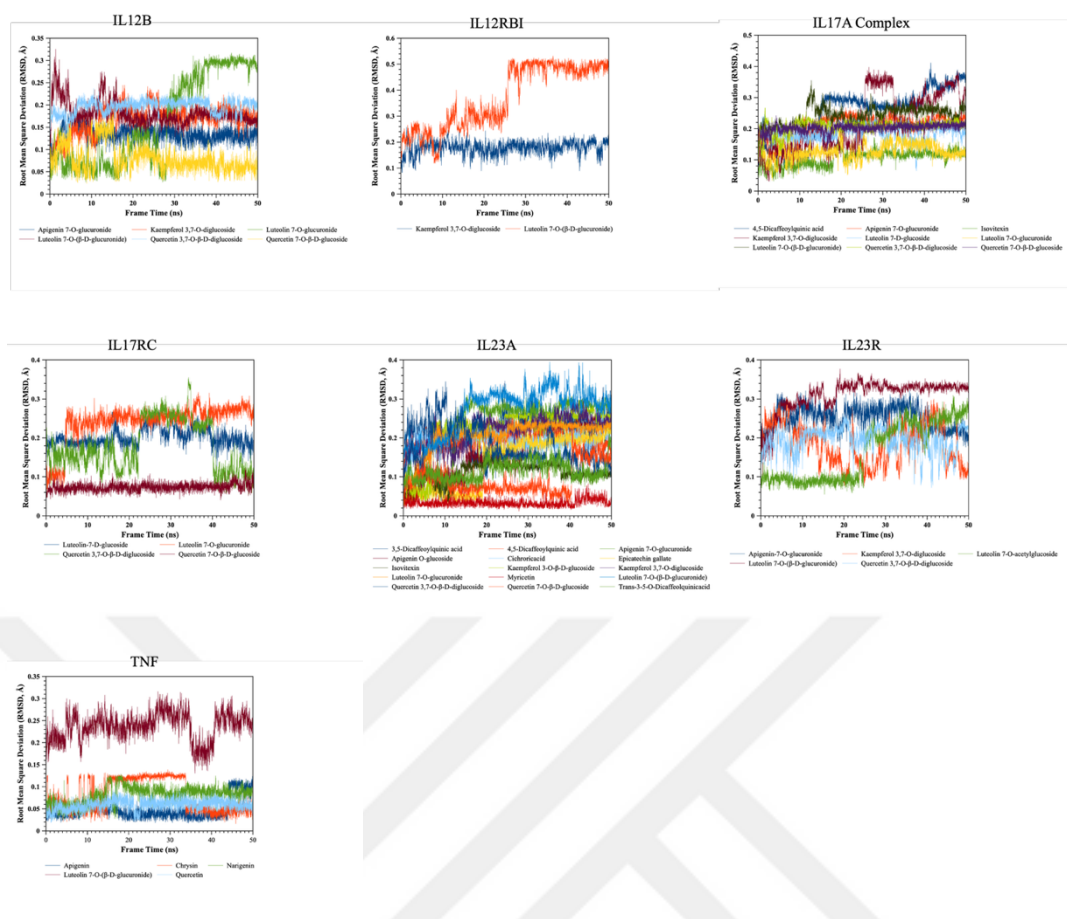
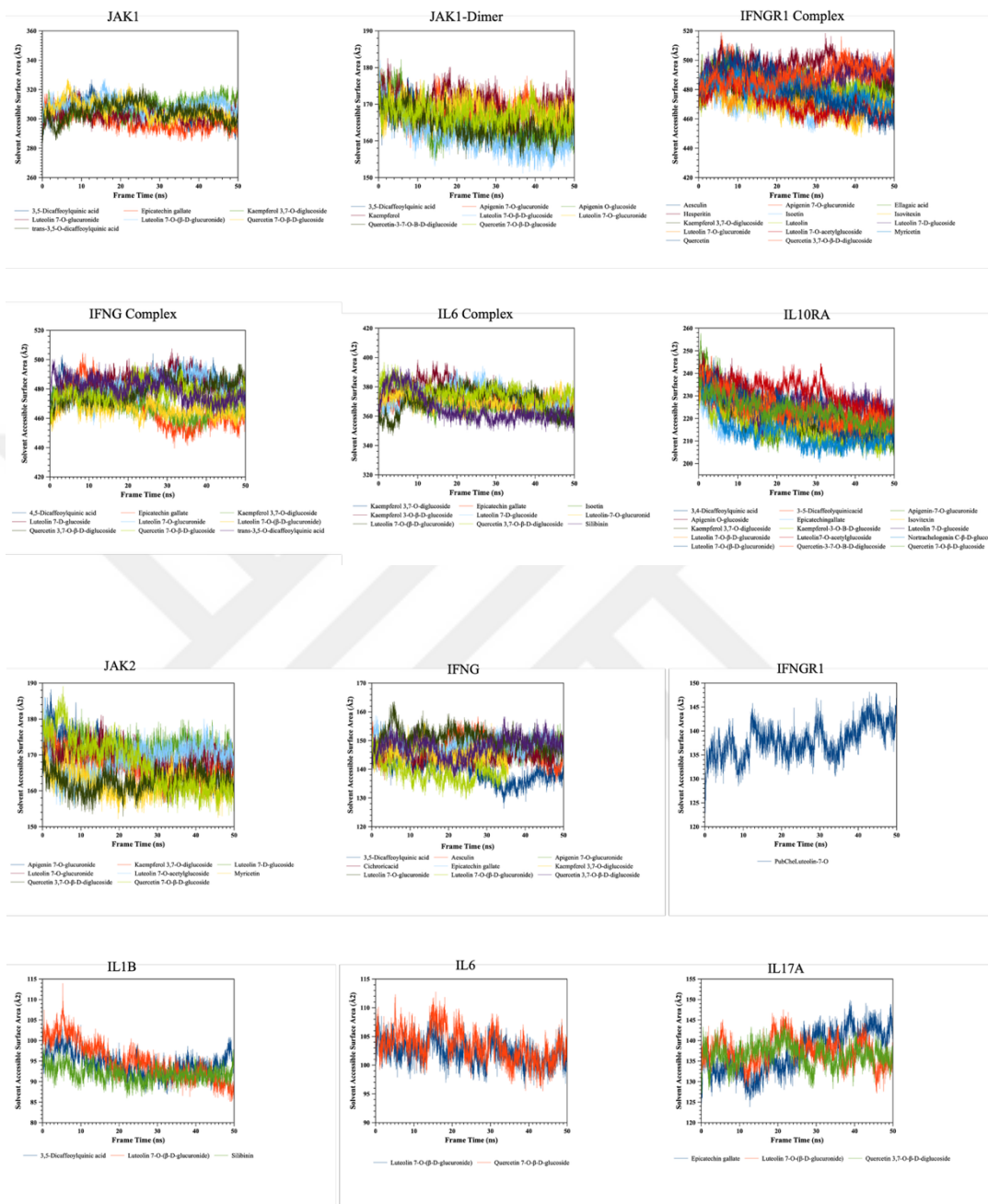


Figure F-1. RMSD Graphs of Ligands Within Protein–Ligand Complexes During Molecular Dynamics Simulations

APPENDIX-G. SASA Analysis



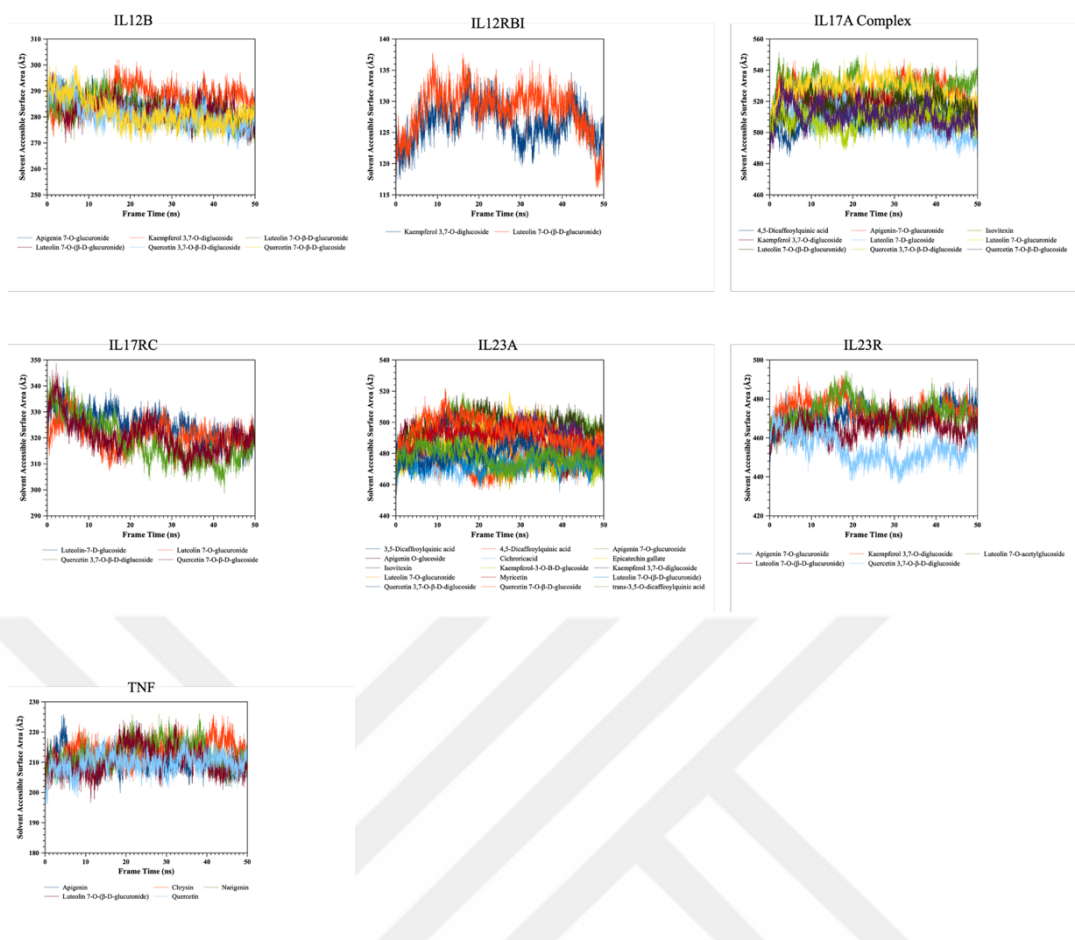
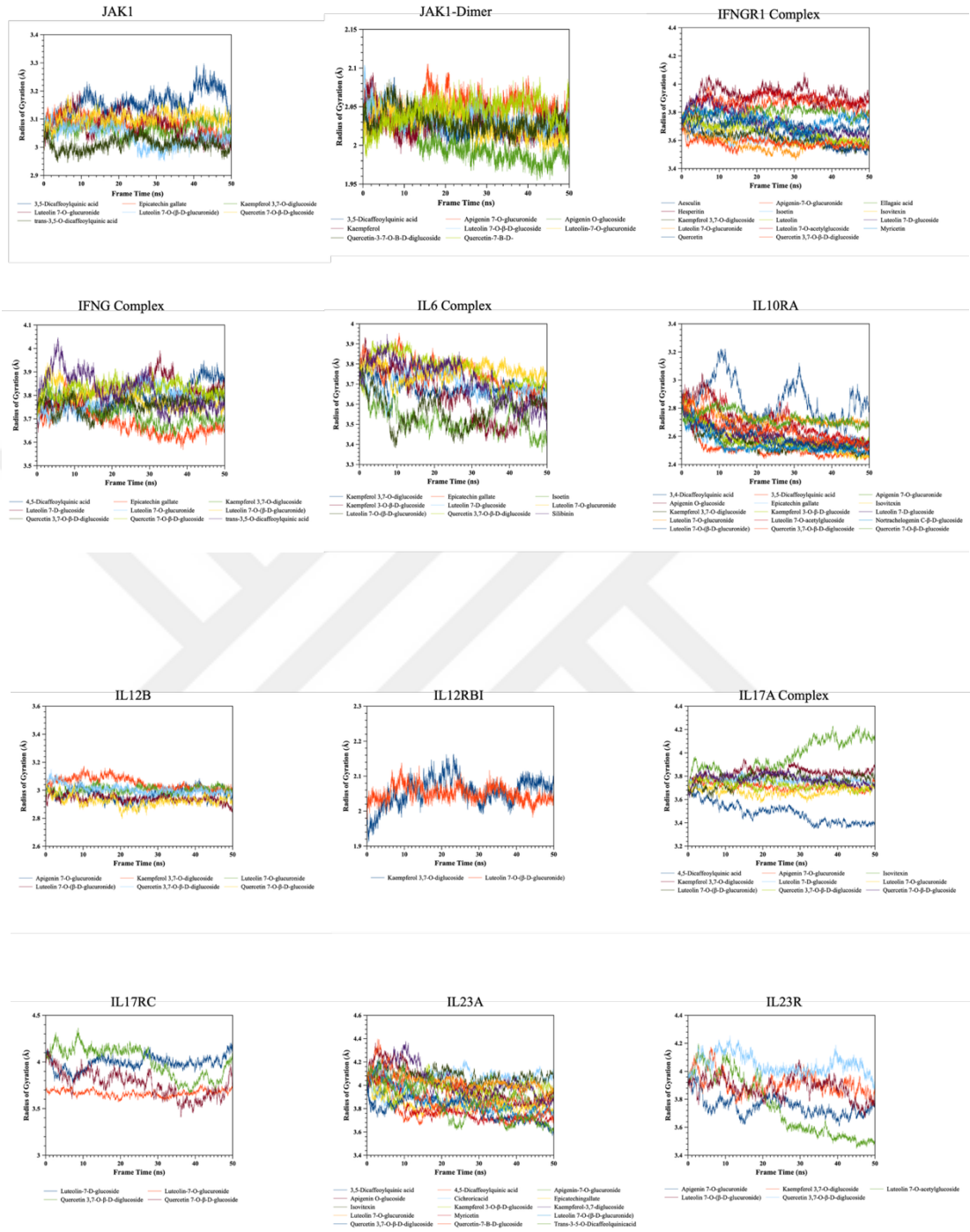


Figure G-1. Solvent Accessible Surface Area (SASA) Graphs of Protein–Ligand Complexes During Molecular Dynamics Simulations

APPENDIX-H. Rg Analysis



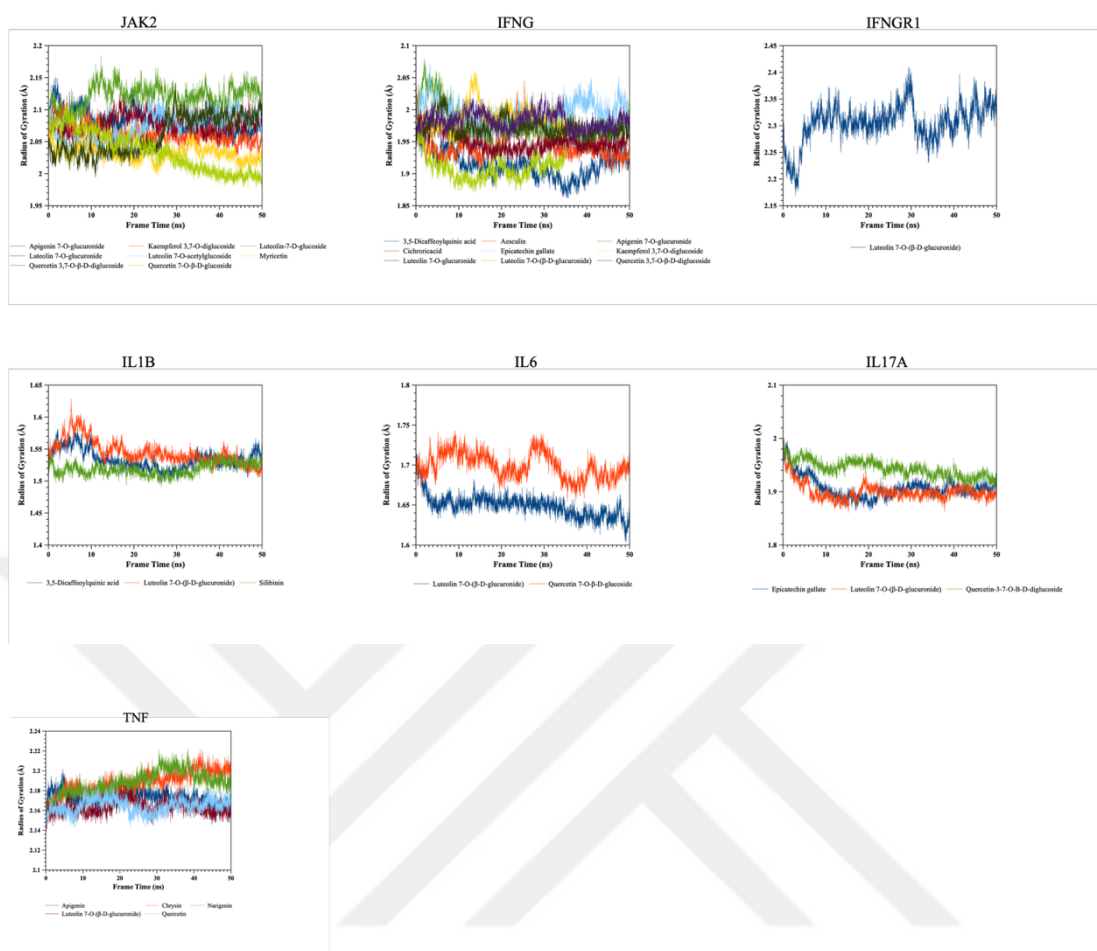


Figure H-1. Radius of Gyration (Rg) Graphs of Protein–Ligand Complexes During Molecular Dynamics Simulations