

Exploration of the Potentials of Silymarin in Atopic Dermatitis with *In Silico* Evidence: An Overview

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Abstract: The recurrent and remitting skin disorder known as atopic dermatitis, or eczema, is caused by immunological dysregulation, environmental variables, and mutations in the epidermal gene that damage the epidermis and cause extremely irritating skin sores. In developed countries, it has been estimated to impact 2% to 10% of adults and 10% to 30% of children. Numerous flavonoid compounds have shown promising results in the treatment of atopic dermatitis, and plant-based flavonoids with their antioxidant, anti-inflammatory, anti-proliferative, and chemoprotective qualities have been investigated. This study offers a comprehensive review of silymarin's function in atopic dermatitis based on the published research that is accessible through the scientific database. In order to find relevant information about the effects of silymarin in atopic dermatitis, 2,352 articles were evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria, which are designed for systematic review authoring. Results: The present work centres on a comprehensive meta-analysis of the scientific literature and the latest available research updates. An effort has been made to compile the pertinent data about the pharmacological and phytochemical features of silymarin, a flavonoid molecule, in the study of skin disorders. In support of the material analyzed in the literature, we conducted an in-silico investigation, the findings of which are discussed in this article.

Keywords: silymarin; atopic dermatitis; eczema; skin barrier dysfunction; skin disorder; cutaneous disease; skin inflammation.

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1. Introduction

Atopic dermatitis (AD), sometimes referred to as atopic eczema, is a common chronic inflammatory skin disorder that is characterized by recurrent eczematous plaques and patches

that cause it to itch [1]. It is a recurrent and remitting skin condition that results from immunological dysregulation, environmental factors, and mutations in the epidermal gene that create disruptions in the epidermis, resulting in extremely itchy skin sores [2]. A range of symptoms, from moderate to severe, is experienced by people of all ages, making it one of the most common inflammatory chronic skin conditions [3]. In developed nations, atopic dermatitis affects between 10% to 30% of children and 2% to 10% of adults. While the incidence of AD has climbed globally over the past 30 years, new evidence indicates that rates may have plateaued in several developed nations like the UK and New Zealand [4,5]. Because of their long history of usage, lower cost, better patient tolerance, and fewer side effects, herbal medications derived from plant sources are popular for treating cosmetic or skin pathological conditions. Remarkably, research on the antibacterial, anti-dermatophytic, antioxidant, anti-inflammatory, anti-proliferative, and chemoprotective properties of herbal medicines against melanoma and non-melanoma skin cancers, dermatophytosis, atopic dermatitis, psoriasis, and acne has been ongoing for a considerable amount of time [6]. The antioxidant, anti-allergic, and anti-inflammatory qualities of plant flavonoids can suppress a number of pathways linked to the development of atopic skin. Atopic dermatitis has shown promising results when treated with a variety of flavonoid molecules based on drug delivery methods [7].

2. Pathophysiological Aspects of Atopic Dermatitis

The pathogenesis of AD is multifaceted, involving genetic predispositions, abnormalities in skin function, immune system dysregulation, and environmental influences. Figure 1 depicts the inflammatory response and breakdown of the skin barrier in atopic dermatitis.

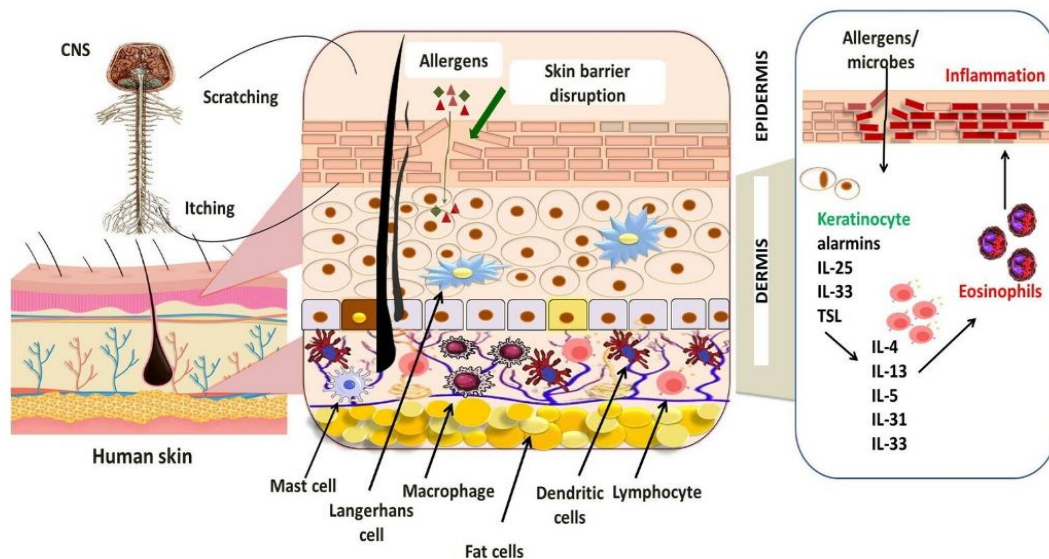


Figure 1. Skin barrier disruption and inflammatory response in atopic dermatitis

2.1. Epidermal barrier dysfunction.

The epidermis of the skin, also known as the skin barrier, shields the interior parts of the body and prevents the transepidermal water loss. The stratum corneum (SC) primarily performs this job; however, the remaining epidermis also helps by creating the SC [8,9]. A complete biological and immunological barrier is provided by the arrangement of SC brick (protein-rich cells called corneocytes) and mortar (mostly lipids such as ceramides, free fatty acids, and cholesterol) model. Keratinocytes secrete the contents of the lamellar bodies that

comprise the mortar as they advance toward the surface to become corneocytes. SC hydration is essential to maintain SC homeostasis. The preservation of natural moisturizing factors (NMF) and the avoidance of water evaporation sustain endogenous hydration. The skin barrier abnormalities in AD are brought on by this imbalance in homeostasis. A permeability barrier impairment is a hallmark of atopic dermatitis (AD) [10,11]. Another factor thought to contribute to the failure of the epidermal barrier is the filaggrin mutation. Many filaggrin metabolites, including pyrrolidone carboxylic acid, sugars, urea, lactic acid, and amino acids, function as natural moisturizing factors (NMF) for the skin, contributing significantly to SC hydration and, consequently, SC homeostasis. The xerosis observed in AD is caused by deficiencies of these substances. Additionally, the metabolites of filaggrin, including pyrrolidone carboxylic acid and urocanic acid, form the acid mantle necessary for optimal functioning of the SC. The keratinocyte cytoskeleton retracts when there is a severe filaggrin deficiency, reducing the quantity of lamellar body lipids that are transported to the mortar [12].

2.2. Immunologic mechanisms.

For the purpose of creating tailored treatments meant to alter immune responses and restore skin barrier function in atopic dermatitis patients, it is essential to comprehend the main immunologic mechanisms underlying the condition.

2.2.1. Th2 cell predominance.

Patients with atopic dermatitis have a higher prevalence of T helper type 2 (Th2) immunological responses. Th2 cells release cytokines, such as interleukin-13 (IL-13), interleukin-5 (IL-5), and interleukin-4 (IL-4), which promote the production of immunoglobulin E (IgE), allergic inflammation, and the recruitment of mast cells and eosinophils in the skin [13,14]. Other subsets of T helper cells, such as Th17 and Th22 cells, are also linked to atopic dermatitis in addition to Th2 cells. A meta-analysis found that peripheral blood from AD patients had a lower percentage of Tregs and a higher number of Th22 cells, Th17 cells, and IL-17 [15]. Th17 cells produce the inflammatory-stimulating interleukin-17 (IL-17), while Th22 cells create the epidermal hyperplasia-causing interleukin-22 (IL-22), which weakens the skin barrier [16].

2.2.2. Dysregulation of cytokines and chemokines.

Numerous chemokines and cytokines are involved in the pathophysiology of atopic dermatitis. These consist of thymic stromal lymphopoietin (TSLP), tumor necrosis factor-alpha (TNF- α), IL-4, IL-13, IL-31, IL-5, IL-6, and IL-22. These are all involved in the augmentation of immune cells, inflammation, and disruption of the skin barrier [17].

2.2.3. Inflammatory cell infiltration.

Eosinophils, mast cells, and dendritic cells are a few of the immune cells that infiltrate the skin in atopic dermatitis [18]. Histamine and other inflammatory mediators are released by mast cells, which exacerbate inflammation and itching [19]. Most eosinophilic dermatoses are associated with allergies, such as urticaria, allergic contact dermatitis, atopic dermatitis, eczema, and allergic drug eruption. Eosinophils are associated with allergic inflammation and tissue damage [20].

2.3. Genetic factors.

Many genetic factors contribute to atopic dermatitis (eczema); gene mutations in particular are important. The essential membrane protein filaggrin (FLG) in skin has been discovered to have the greatest genetic association with AD. AD is known to occur from a variety of different hereditary abnormalities, including cornified lipid envelopes and lamellar membranes. Netherton syndrome is a case in point. Table 1 below lists the major gene mutations and known genetic variants linked to atopic dermatitis.

Table 1. Genetic mutations involved in Atopic dermatitis.

Gene	Function	Effect of mutation	Reference
Filaggrin (FLG)	Skin barrier protein that preserves the integrity of the skin	Due to their effect on the skin barrier function, FLG mutations raise the risk of atopic dermatitis by potentially increasing trans-epidermal water loss, altering pH levels, and dehydrating the skin. Further bacterial colonisation in disrupted skin leads to inflammatory cascades.	[21-23]
SPINK5	A serine peptidase inhibitor that controls the epidermal barrier	Mutations in SPINK5 lead to a deficit in its processed protein LEKTI, which causes Netherton syndrome, characterized by severe eczema-like symptoms.	[24,25]
CARD11	Immune signalling and controlling inflammation	The mutation of these genes significantly affects inflammation and immunological responses. There are changes in the homeostasis of human natural killer cells leading to a compromised immune system, as well as increased susceptibility to viruses.	[26,27]
IL4/IL13 genes	Cytokines that are part of the immune response	Variations significantly impact the risk of eczema and the development of the skin barrier. Patients with atopic dermatitis have higher IL-4R α R576 polymorphism. Similarly, the coding region of <i>IL-13 variant</i> is functionally related to high total serum IgE level and atopic dermatitis.	[28,29]
Interleukin-31 receptor A (IL-31RA)	IL-31 cytokine receptor; itchy feeling	AD triggers the release of large amounts of TH2-associated cytokines, such as IL-31, by activation of the heterodimeric receptor IL-31 receptor A. These cytokines stimulate itching, initiate immunoregulatory circuits, drive inflammatory responses, and encourage neuronal growth.	[30,31]
Thymic Stromal Lymphopoietin gene (TSLP)	A cytokine that stimulates the immune system and inflammation	Thymic stromal lymphopoietin is one link between the weakened skin barrier and the control of a T-helper (Th) ₂ response. Thymic stromal lymphopoietin (TSLP), a cytokine, has been shown to play a role in immune homeostasis maintenance and type 2 inflammatory response modulation at mucosal barriers in allergic inflammation.	[32,33]
OVOL1/OVOL2	Involved in the development and differentiation of the skin barrier	The development of epithelial tissues produced from germ cells depends on these genes. The OVOL1-OVOL2 axis controls the development and proliferation of human keratinocyte cells. Furthermore, it has been shown that OVOL1 plays a crucial role in the expression of epidermal barrier proteins, including filaggrin (FLG), and that its mutation or dysfunction results in atopic dermatitis (AD).	[34]

3. Materials and Methods

Various databases, including PubMed and Science Direct, were used to search and collect relevant literature. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria recommended for drafting methodical reviews were followed. The major keywords, such as ‘silymarin in Atopic dermatitis’, ‘silymarin in eczema’, ‘silymarin in skin inflammation’, ‘silymarin in cutaneous inflammation’, ‘silymarin clinical trials Atopic dermatitis’, were used during the search of the literature in various databases. Initially 2, 352 articles were collected through electronic database search; irrelevant titles/ abstracts and other types of articles (2,306) were excluded. Out of 46 assessed reports, 05 duplicate articles were

excluded. Finally, 41 articles were included in this narrative review as represented in the flow chart (Figure 2).

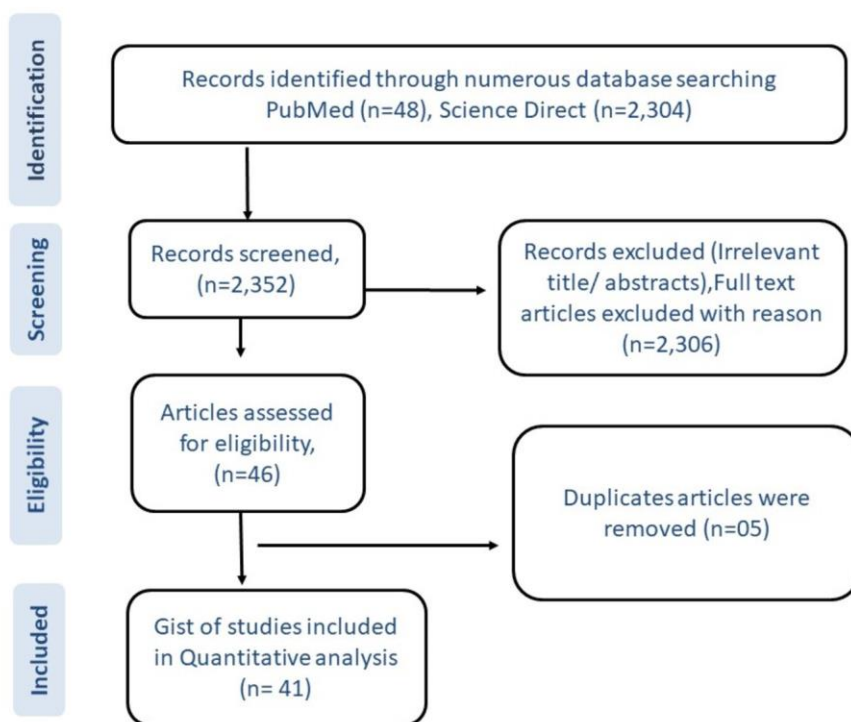


Figure 2. PRISMA flow diagram for screening and selection of literature.

4 . Results and Discussion

4.1. Natural occurrence of silymarin and related compounds (isomers).

Two stereoisomers known as silibinin A and silibinin B make up the majority of silymarin (about 60–70%). Silicitrin, silidianin, and isosilibinin are the next most common forms of silymarin. Silymarin and its components are safe and powerful antioxidants with detoxifying, preventive, protective, and regenerative properties. Traditionally, silymarin-enriched plant *Silybum Marianum* L. (Milk thistle) has been used for centuries for the treatment of different diseases such as liver and gallbladder disorders, protecting the liver against snake bite and insect stings, mushroom poisoning, and alcohol abuse [35,36]. Although the composition of silymarin can vary for a variety of reasons, silibinin is known to make up the majority of the combination (about 50%), and as a result, a large portion of the mixture's biological activity is attributed to this molecule [37].

4.2. Mechanistic role of silymarin in atopic dermatitis.

The medicinal properties of silymarin, which is extracted from milk thistle (*Silybum marianum*), have been investigated in relation to atopic dermatitis (eczema), a chronic inflammatory skin disorder. Numerous studies have shown how silymarin can be used to treat a variety of dermatological conditions, including leishmaniasis, erythema and skin whitening, melasma, rosacea, psoriasis, atopic dermatitis, acne, wound healing, and protection from UV rays and sunburns. These conditions are all biologically related to silymarin's anti-inflammatory, antioxidant, and anti-proliferative qualities [38,39]. Silymarin is an interesting component for cosmetic and dermatological applications because of its several effects, which

are connected to its activity on the skin. An outline of silymarin's potential use in the treatment of atopic dermatitis is provided in Figure 3 and discussed below.



Figure 3. Pharmacological potentials of silymarin in atopic dermatitis.

4.2.1. Anti-inflammatory properties.

Research has demonstrated that silymarin, through regulating the release of cytokines and the infiltration of neutrophils, is a significant anti-inflammatory agent. Silymarin exhibits anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and lipoxygenase and cyclooxygenase [40]. These cytokines are involved in the inflammatory processes that contribute to the development and exacerbation of atopic dermatitis. Among the phenolic chemicals obtained from plants, silymarin has been shown to have wound-healing properties [41]. In a randomized, double blind, placebo-controlled study of patients with chemotherapy-induced oral mucositis, silymarin's anti-inflammatory qualities were found to hasten the healing process [42]. Research has indicated that flavonoids function by regulating multiple molecular pathways linked to inflammation, cytokine generation, and keratinocyte proliferation, and several phenolic compounds, including silymarin, have shown wound healing effects [41,42]. In a study investigating the function of silymarin in reducing inflammation and promoting epidermis regeneration, flavonoid 2, 3-dehydrosilybin (DHSB) was found to downregulate the production of numerous pro-inflammatory cytokines (IL-1, IL-6, and IL-8) by normal human epidermal keratinocytes (NHEKs) [43,44]. The results of the study demonstrated that topical silymarin therapy improved the healing capacity of rats' wounds, as seen by a reduction in exudates, edema, and redness, suggesting that it is a promising therapeutic agent with anti-inflammatory qualities [45]. The ability of silymarin to significantly reduce gelatinolytic activity in vitro raised the possibility that it could be used to treat inflammatory skin conditions by blocking gelatinase activity, as evidenced by the gelatinase inhibition assay in HaCaT cells and the in vivo study in mice using a model of cutaneous inflammation mediated by reactive oxygen species [46]. Silibinin is thought to protect human foreskin fibroblasts against UVB-induced inflammation, cell death, and senescence by increasing nuclear estrogen receptor α and β in fibroblasts treated with UVB [47]. Normal human epidermal keratinocytes (NHEKs) were treated with lipopolysaccharides (LPS) and sodium dodecyl sulfate (SDS) to generate inflammation in order to determine

whether or not silymarin components encouraged epidermis regeneration and reduced inflammation. According to the findings, dehydrosilybin (2, 3-DHSB) prevented NHEKs from producing certain pro-inflammatory cytokines [43]. A key transduction mechanism involved in cellular functions such as growth, proliferation, and survival is the phosphoinositol-3 kinase (PI3K)/protein kinase B (AKT) signaling system. However, atopic dermatitis, psoriasis, and acne are among the skin conditions caused by aberrant activation of the PI3K/AKT pathway. The silymarin-rich milk thistle extract has been reported to exert anti-inflammatory properties by NF- κ B/IL-23/IL-17A suppression [48].

4.2.2. Antioxidant activity.

Oxidative stress plays a role in the pathogenesis of atopic dermatitis, contributing to skin barrier dysfunction and inflammation. Silymarin's antioxidant properties help neutralize free radicals and reduce oxidative damage in the skin, potentially mitigating inflammation and supporting skin barrier integrity [49-52]. With detoxifying, preventative, protective, and regenerating qualities, silymarin and its constituents are safe and effective antioxidants. Owing to its antioxidant qualities, silymarin has been identified as an important natural compound for topical photo protection [53]. In addition to having potent antioxidant and UV-protective properties for the skin, silymarin and milk thistle fruit extract may block the enzymes responsible for the breakdown of extracellular matrix components [54]. Pretreatment with SM produced a noteworthy neuroprotective action against TMX-mediated brain damage, indicating its promising antioxidant and anti-inflammatory actions. This study examined the neuroprotective effects of SM against TMX-triggered cortical injury in male rats. The inhibition of excess free radicals and the generation of inflammatory cytokines, along with Nrf2/NF- κ B/iNOS signaling, were proposed to be the mechanisms underlying this impact [55]. By preventing free radicals from lipid peroxidation and myeloperoxidase and sparing catalase, glutathione peroxidase, and epidermal superoxide dismutase (SOD), silibinin has been reported to serve as an antioxidant [56].

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4.2.4. Skin barrier enhancement.

Silymarin promotes the synthesis of ceramides and other lipids essential for maintaining the skin barrier function. Strengthening the skin barrier is crucial in atopic dermatitis to prevent allergens and irritants from penetrating the skin and triggering immune responses. Silibinin, one of the major active constituents of silymarin extracted from Milk thistle (*Silybum marianum*), is bioactive, and topical formulations containing silymarin inhibit UVB irradiation-induced oxidative stress in guinea pig and Human Adult Keratinocyte cell line (HaCaT keratinocytes) [57,58]. According to a paper, pretreatment with silymarin restores the lowered lipogenic gene expression in imiquimod-treated mice to normal levels, suggesting that silymarin may enhance the function of the skin barrier. As a result, SM effectively reduced dermal-infiltrating cells, parakeratosis, hyperkeratosis, and epidermal thickness [59].

4.2.5. Immunomodulatory effects.

Silymarin's numerous immunomodulatory effects are well-known, mostly due to its antioxidant, anti-inflammatory, and liver-protective properties. It has been claimed that silymarin inhibits the formation of skin malignancies and photocarcinogenesis by immunomodulation in conjunction with antioxidants, anti-inflammatory agents, and apoptosis. Another benefit is that it is nontoxic even at dosages higher than physiological concentrations [60]. Through its effects on different immune cells and inflammatory signaling pathways, it modifies immune responses. It might lessen skin inflammation and alleviate symptoms by regulating the aberrant immune response associated with atopic dermatitis. Silymarin/silybin has immunomodulatory effects and is both immunostimulatory and immunosuppressive. The capacity of the silymarin treatment to reverse UVB-induced immunosuppression has been associated with decreased IL-10 production in UV-irradiated skin and draining lymph nodes [61]. As an immunomodulator, silymarin inhibits T-lymphocyte function at low concentrations and triggers inflammatory responses at high concentrations [62].

4.3. Clinical studies.

There are currently relatively few clinical trials available to confirm silymarin's efficacy and safety in treating atopic dermatitis in humans. The severity and symptoms of AD were shown to be considerably reduced in 40 patients with mild to moderate eczema who participated in a randomised double blind controlled clinical trial [63]. Another randomized, double-blind, placebo-controlled clinical study evaluated silymarin 1% gel's ability to prevent radiodermatitis occurrences in comparison to a placebo. Forty patients randomly received silymarin gel or a placebo formulation on the chest wall skin following modified radical mastectomy, once daily starting on the first day of radiotherapy for 5 weeks. There was a delay in radiodermatitis development and progression in the silymarin group [64].

4.4. In silico computational analysis.

In support of the above-discussed research works related to the therapeutic potential of silymarin against atopic dermatitis, a computational analysis has been performed by screening silymarin isomers against various therapeutic targets concerned with the pathophysiological

progression of atopic dermatitis to identify the most potent silymarin isomer as well as the most probable mechanism of action involved for the same. The utilized docking process for all the concerned therapeutic targets involved in the pathophysiology of atopic dermatitis was validated by considering the obtained binding energies, chemical resemblance, and overlay of the reference ligand. For successful validation of the docking protocol, the binding energy should be within the range of -5 to -15 kcal/mol, with similar binding interactions and binding conformations to those of the reference ligand, with root mean square deviation (RMSD) within the range of 3Å. In the current research paradigm, all the docking protocols for TRPA1, filaggrin, JAK-2, SIRT-1, and TSLP were successfully validated, as their binding energies and RMSD values are observed within the prescribed range. The docking-based *in silico* screening of silymarin isomers was performed by using Autodock 4.2 [65-68] software against concerned therapeutic targets for atopic dermatitis, including transient receptor potential ion channel TRPA1, filaggrin, JAK2, SIRT1, TSLP, etc., after validating the utilized docking protocols [69-71]. The docking-based screening results for silymarin isomers against various considered therapeutic targets for atopic dermatitis are tabulated in Table 2.

Table 2. Docking-based screening results for silymarin isomers against various therapeutic targets for atopic dermatitis.

S. No.	Ligand	Binding energy (kcal/mol)				
		TRPA1 (pdb: 6v9v)	Filaggrin (pdb: 4pcw)	JAK-2 (pdb: 2b7a)	SIRT-1 (pdb: 5btr)	TSLP (pdb: 8qfz)
1	Isosilibinin A	-6.19	-6.97	-7.54	-6.68	-5.41
2	Isosilibinin B	-6.77	-5.03	-6.58	-7.65	-5.82
3	Silibinin A	-7.9	-5.60	-8.15	-7.46	-6.83
4	Silibinin B	-6.74	-5.84	-6.76	-7.80	-5.97
5	Silicitrin	-6.53	-4.84	-7.41	-7.01	-5.53
6	Silidianin	-6.66	-5.74	-7.75	-7.80	-6.95
7	Taxifolin	-5.7	-6.12	-7.34	-5.61	-5.92
8	Delgocitinib	-6.8	-4.72	-7.52	-6.64	-6.90

The docking-based screening has concluded that the therapeutic effect of silymarin against atopic dermatitis was due to its most potent constituent, silibinin A, via interaction with the JAK2 receptor. The two-dimensional binding interactions and three-dimensional binding conformation of silibinin A with JAK2 were depicted in Figure 4.

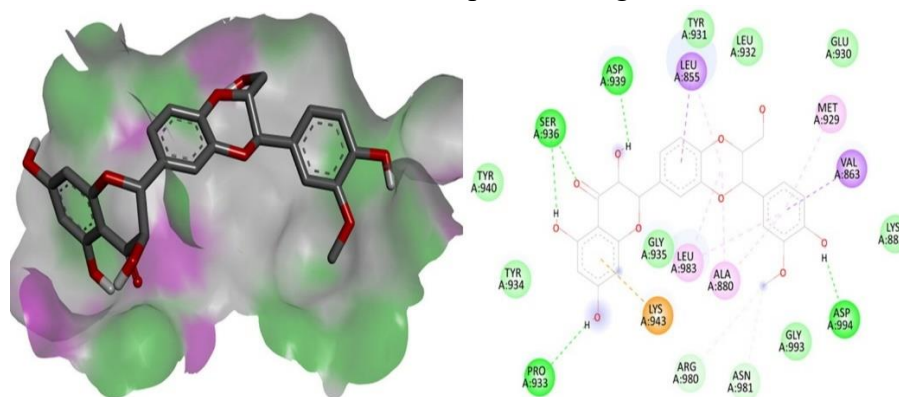


Figure 4. Two-dimensional binding interactions and three-dimensional binding conformation of silibinin A with JAK2 receptor.

Therefore, to confirm the same MD simulation of the macromolecular complex of silibinin A within the active binding cavity of JAK2 receptor was performed for 100 ns by using Desmond software by Schrodinger to validate their thermodynamic stability [72-75]. The MD simulation has revealed that the macromolecular complex of silibinin A within the active

site of JAK2 receptor was highly stabilized throughout the simulation [76,77]. The observed root mean square deviation (RMSD) and binding interaction for silibinin A against the JAK2 receptor observed during the simulation are depicted in Figures 5 and 6, respectively.

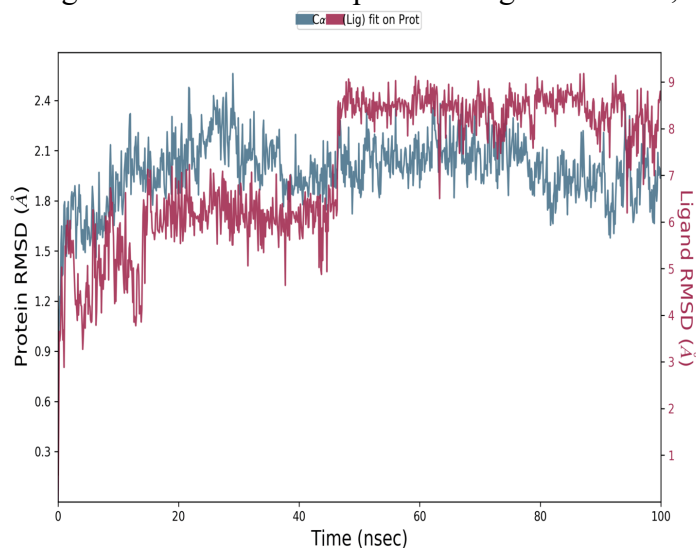


Figure 5. RMSD observed for silibinin A-JAK2 complex during 100 ns MD simulation.

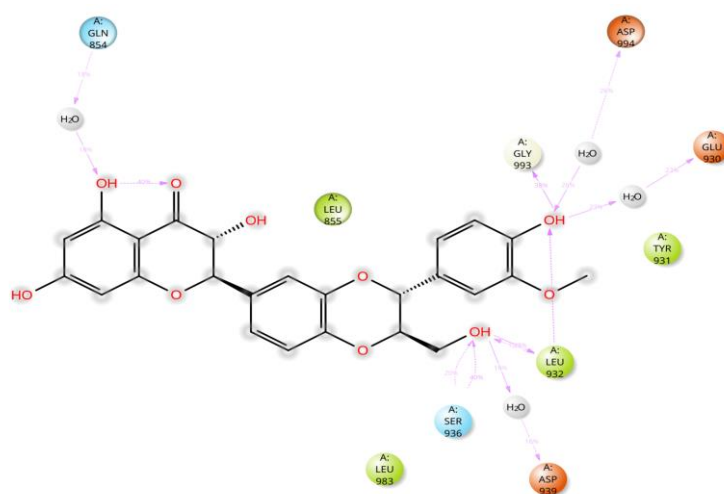


Figure 6. Two-dimensional binding interactions observed during a 100 ns MD simulation for the silibinin A-JAK2 complex.

It has been concluded by the performed *in silico* analysis that silibinin A is interacting strongly with the human JAK2 receptor, with the highest binding energy compared to other concerned therapeutic targets for atopic dermatitis in the current study, as well as being highly stabilized within the target macromolecular cavity. The previously reported anticancer potential of silibinin A should be due to its interaction with the human JAK2 receptor and needs to be verified experimentally to open up the newer therapeutic possibilities for atopic dermatitis. These computational findings have concluded that the flavonoidal compound silibinin A is supposed to be the most active constituent of the silymarin plant for executing therapeutic potential against atopic dermatitis via interacting with the JAK2 receptor.

5. Conclusions

Based on the results of literature screening and preliminary *in silico* evidence, silymarin appears to be a promising candidate for atopic dermatitis. Silymarin has substantial promise

for future *in vitro* and *in vivo* testing. Its safety profile and diverse bioactivities make it a strong candidate for development into therapies targeting skin disorders. However, better formulation, mechanistic understanding, and clinical translation strategies are needed to fully realize its potential. Though a substantial number of pre-clinical reports are available, the dearth of clinical data in humans provides ample scope to explore its potential in eczema.

Author Contributions

Conceptualization, U.K.; methodology, A.K.; S.M.; D.K.C.; writing—review and editing, A.K.; visualization, N.C. and S.R.M.; supervision, U.K.. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

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Data Availability Statement

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

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Conflicts of Interest

The authors declare no conflict of interest.

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