

Plumbagin and Resveratrol through Their Anti-Inflammatory and Multi-Target Modulatory Potential Ameliorate UV-Induced Psoriasis-Like Conditions in Rat

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Abstract Introduction: Psoriasis is an autoimmune, progressive, and chronic inflammatory condition predominantly caused by various inflammatory and immunological mediators. Phytochemicals, such as plumbagin (PL) and resveratrol (RSV), have anti-inflammatory, antioxidant, and immunomodulatory properties. **Methods:** The induction of psoriasis-like conditions in rats was standardized by exposing them to ultraviolet (UV) radiation for 30 minutes on their dorsal skin surfaces. The psoriasis area severity index (PASI) scoring was utilized to confirm the psoriasis induction. Biochemical measurement of the hydroxyproline (HP) content was performed to measure collagen rupture, accompanied by histological evaluation of the exposed area. The Swiss Dock web server was used for the in silico docking of mammalian targets of rapamycin (mTOR), fibro-collagenase, and nuclear factor kappa B proteins. **Results:** A 30-minute UV exposure was standardized and created as a model for inducing psoriasis-like conditions. Administration of PL and RSV alone or in combination restored the increased PASI score within a week and hastened recovery. These medications also limited the increase in the HP content and altered the morphology. The combination of PL with RSV is more effective than either medicine alone. In silico docking, the analysis

demonstrated that PL and RSV had a good binding relationship with mTOR, NF- κ B, and fibro-collagenase. **Conclusion:** UV exposure for 30 minutes causes a psoriasis-like state, whereas PL and RSV prevent the production and progression of psoriasis-like conditions via their multi-target modulatory mechanisms. Target-specific investigations require molecular-level research.

Keywords Psoriasis, Plumbagin, Resveratrol, UV-Induced Psoriasis, Molecular Docking

1. Introduction

Psoriasis is a chronic illness significantly affecting about 2-3% of individuals who experience various psoriatic symptoms, viz., scales, itching, and redness. This affects them physically and emotionally, resulting in a substantial reduction in the quality of patient life [1]. Various factors, including genetic makeup, ethnicity, stress, sedentary lifestyle, infections, alcoholism, and smoking, are involved in the pathology of psoriasis. Additionally, increased epidermal thickness, immune cell infiltration, keratinocyte differentiation, and hyperproliferation contribute to

psoriasis [2], [3]. Psoriasis is associated with psoriatic arthritis, anxiety, depression, and cardiometabolic syndromes [2]. Psoriatic patients have a higher chance of experiencing comorbid conditions such as anxiety, depression, schizophrenia, and suicidal ideation with an increased level of interferon (IFN)- γ , nuclear factor (NF)- κ B, tumor necrosis factor (TNF)- α , signal transducer activator of transcription (STAT)-3, and cytokines than normal individuals [4], [5]. The inhibition of these factors has emerged as a beneficial approach for the management of psoriasis [4]. An imbalance in endogenous oxidants and antioxidants, such as elevation of malondialdehyde (MDA) and reduction of catalase, contributes to psoriasis [6], [7], [8], [9]. Acute ultraviolet (UV) exposure induces DNA damage and erythema, whereas prolonged exposure causes mutations and immunosuppression [6], [9]. Studies have shown that persistent exposure to UV radiation (315 nm) can cause epidermal damage and trigger the release of prostaglandins that induce pain and inflammation [10]. This damage also causes the breakdown of collagen and the liberation of hydroxyproline (HP). It acts as a marker of psoriasis [11].

Topical and systemic medications are available for anti-psoriatic therapy, which may have adverse effects, such as itching, irritation, redness, and discoloration. Salicylic acid possesses keratolytic, antimicrobial, analgesic and anti-inflammatory effects at significantly higher doses than its anti-psoriatic dose but produces salicylism [12]. Salicylates, methotrexate, apremilast, acitretin, cyclosporine, corticosteroids, and glucagon-like peptide-1 are used to suppress inflammation and immunomodulation associated with psoriasis [13], [14], [15]. The current immunotherapeutic approach focuses on the use of TNF- α , interleukin (IL)-23, and IL17 antibodies for the treatment of psoriasis [16], [17].

Traditional plant-based medications are popular, and hence, as allopathic alternatives, herbal formulations have gained importance because of their affordability, tolerability, effectiveness, and fewer side effects [2], [3], [18], [19]. Kjaer et al. found that using three biologically active ingredients might help control psoriasis [5], [20]. In our earlier research, plumbagin (PL) and RSV demonstrated synergistic analgesic and anti-inflammatory

effects through their antioxidant properties and ability to modulate multiple targets. The current study aimed to induce psoriasis-like conditions using UV radiation, followed by pharmacological, biochemical, and *in silico* evaluations of PL and RSV, individually and in combination.

2. Material and Method

2.1. Drugs and Chemicals

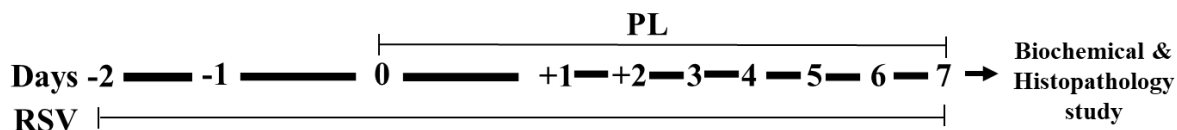
Current work utilized the following materials: plumbagin (PL; 98%; PC Chem, Mumbai), resveratrol (RSV; 98%; Sherate Nutrition), acetylsalicylic acid (Loba Chemical), thiopentone (Thiosol), paraformaldehyde, EDTA, Lobet S (Abbot Pharma), Veet (Reckitt Benckiser), dimethyl sulfoxide (DMSO; Loba Chemical, Mumbai), and Ellman's reagent (Loba Chemicals).

2.2. Animal and Ethical Approval

The Wistar rats (180 to 230 g) of either sex (Kusum Life Science, Hingoli (M.S.), India) were maintained in controlled laboratory environments (12h light and 12h dark rotation; temperature: $25 \pm 2^\circ\text{C}$; % humidity: 50–70), while food as well as water was allowed to access *ad libitum*. Animal care was performed according to CCSEA guidelines. The study protocol (Reg. No. IAEC/PJLCP/2021/01) was sanctioned by the Institutional Animal Ethical Committee.

2.3. Study Design and Drug Treatment

The animals were divided into various groups including control (vehicle), induction, PL (1 and 2 mg/kg; *i.p.*), RSV (25 and 50 mg/kg; *i.p.*), standard (Lobet S. 350 mg/rat), and PL+RSV. RSV was administered on days -2, -1, and 0 until day 7, whereas PL was administered on day 0 until day 7 in the respective groups of rats. Biochemical and histopathological examinations were performed immediately after treatment on day 7.



2.4. Induction and Standardization of the Method

An in-house-built UV exposure chamber with a T-shaped design was constructed using a PVC pipe (completely opaque and dark black from the outside). The hairs on the dorsal body surface of the control and induction group rats were removed using a hair removal cream. A predetermined region measuring 2 cm², located at the center of the instrument, was subjected to UV light exposure for 15, 30, and 45 minutes [21]. This exposure occurred 25 cm from the UV light source, specifically emitting light with a wavelength of 395 nm. Group one was the control group and was not exposed to UV radiation. After the irradiation process, the rats were meticulously observed to detect any alterations in the irradiated area, such as the presence of skin lesions and any potential changes in their behavior. In this preliminary investigation, it was observed that the 30-minute duration had a substantial impact on the development of erythema, which was considered for further exploration.

2.5. Macroscopic Examination

Psoriasis-induced rats were visually examined as described by Nagar et al. 2016 using severity index (SI) scales and psoriasis area severity index (PASI) scores ranging from 0 (lowest) to 3 (highest): 0-none (clear), 1-mild (redness), 2-moderate (redness and erythema); and 3-severe (redness, erythema, and scaling) [21].

2.6. Determination of Hydroxyl-Proline Content

HP was estimated using the method described by Patil et al. [22]. Briefly, tissue samples from the respective groups of animals were hydrolyzed using 6N hydrochloric acid (HCL) for 3 h, followed by neutralization. The test tubes, including samples, standards, and blank solutions, were labeled appropriately and visibly. One milliliter (mL) of the test, deionized water, and standard solutions were mixed with 1 mL of a 0.01 molar copper sulfate solution, followed by 1 mL of a 2.5N sodium hydroxide solution and 1 mL of hydrogen peroxide (H₂O₂). This solution was heated to 80°C followed by cooling to room temperature. In addition, 4 mL of 3 N sulphuric acid was added under continuous stirring. Next, 2 mL of p-(dimethylamino) benzaldehyde was heated at a temperature of 70°C for 15 minutes in a water bath. Subsequently, the absorbance of the resultant solution was measured at a wavelength of 540 nm relative to the sample [22], [23].

The sample concentration was calculated as:

$$\text{The conc. (sample)} = \frac{\text{Optical density of the sample}}{\text{Optical density of standard}} \times \text{Conc. of standard}$$

2.7. Histopathological Examination

With slight modifications, histopathological

examination was performed as per the procedure described by Sakai et al. and Sun et al. [24], [25]. Briefly, animals were euthanized with an overdose of thiopentone sodium (70 mg/kg). Skin tissue samples from each group were collected and stored in a formalin solution (10%). A longitudinal segment of the skin measuring 5 mm in thickness was obtained using microtomy techniques. The respective sections were critically stained by hematoxylin and eosin dye. The thickness of the cellular component of the epidermis was measured using a calibrated micrometer [24], [25].

2.8. In-Silico Docking

The Swiss Dock online server was used to study the selected receptor-ligand interactions. The codes for PL and RSV were obtained from the zinc-14 site, and a protein data bank (PDB) was used to select the PDB codes for mTOR, fibro-collagenase, and NFκB [26]. The UCSF Chimera software was used to enhance the visualization and study of ligand-protein interactions [27].

2.9. Data Analysis

The study employed GraphPad Prism (software, V.5.0.) for data analysis, including “one and two-way ANOVA followed by post hoc Bonferroni's multiple comparison tests” for the respective parameters. The study data were represented as the mean of respective parametric values and P<0.05 was considered as significant.

3. Results

3.1. Induction and Standardization of Psoriasis-Like Condition

UV exposure for 15 minutes showed mild signs of erythema from day 4, which was not sufficient (mean PASI score less than 2) to mimic sustained erythrodermic psoriasis-like conditions. While 30 minutes of exposure produced severe erythema, no significant difference was observed between 30 and 45 minutes of UV radiation exposure. Amongst the 15, 30, and 45 minutes of UV radiation exposure for 30 minutes, significant induction (two-way ANOVA, P<0.0001, F_{3, 320} = 184.22) of erythema, which is an erythrodermic psoriasis-like condition, was observed. This induction group, without treatment, required 16 days to normalize (Figure 1A, 1B, & 1C).

3.2. Effects of PL and RSV Alone and in Combination on UV-Induced Psoriasis-Like Symptoms in Rats

As shown in Fig. 2, a 30-minute duration of UV exposure after 6 h significantly triggered a psoriasis-like

condition in rats, as evaluated through the assessment of the PASI score when compared with the group of control rats (two-way ANOVA, $P < 0.0001$, $F_{7, 440} = 357.6$). The hardness of the induction group peaked on day 8, after which it gradually declined and returned to normal levels

by day 16. All treatment modalities, including PL (1 mg/kg at 72 h, $P < 0.001$), PL 2 mg/kg (48 h onward, $P < 0.001$), RSV 25 mg/kg (day 6 onward, $P < 0.001$), 50 mg/kg (48 h onward, $P < 0.001$), and PL 1 mg/kg + RSV 25 mg/kg (72 h onward, $P < 0.0001$) tended to mitigate these effects.

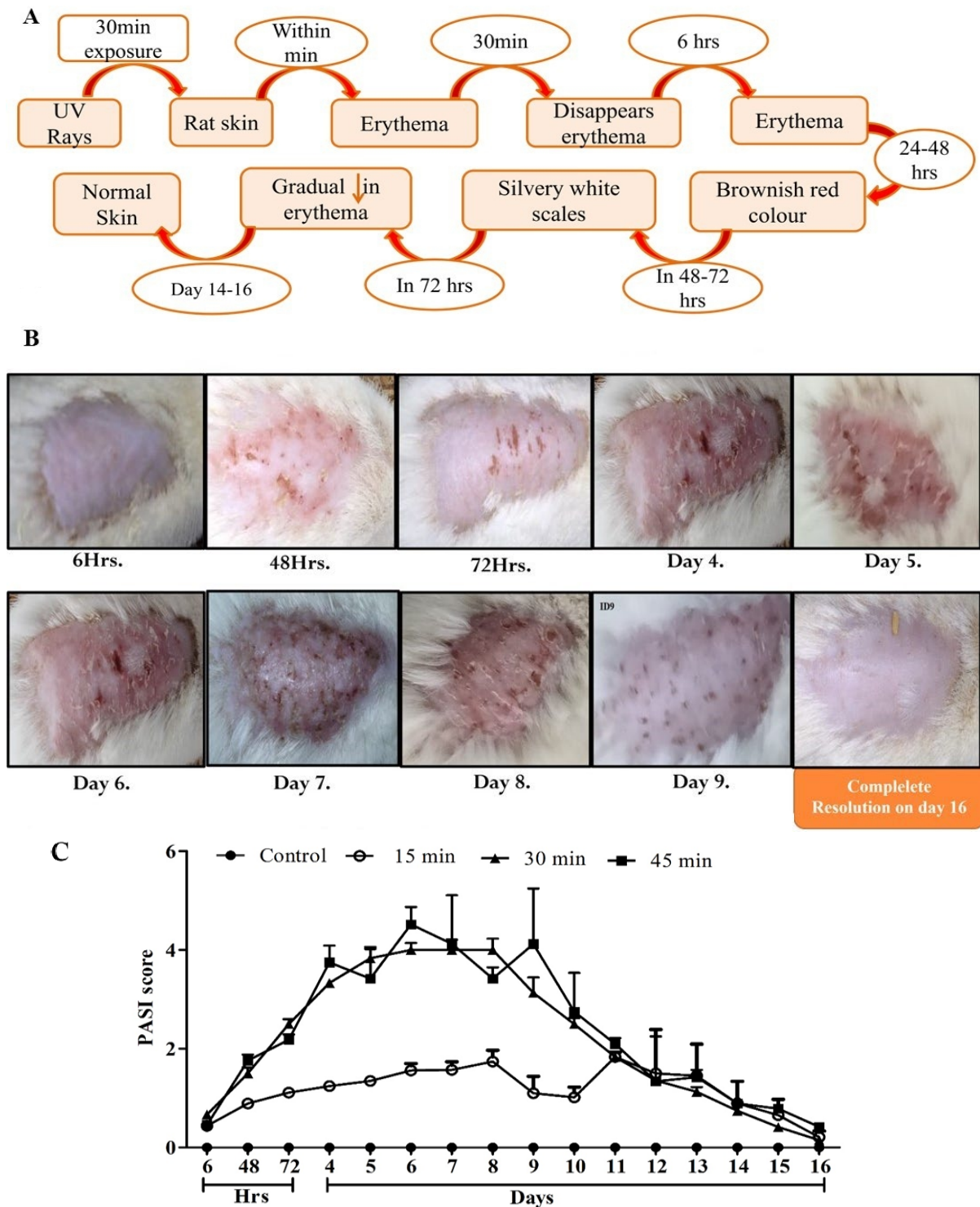


Figure 1. A. Induction of psoriasis using UV rays. B. and C. Day-wise changes in rats after UV light exposure. “The data is expressed on the graph as Mean \pm SEM for each group ($n=6$) and analysed by “two-way ANOVA followed by the post hoc Bonferroni’s multiple comparison test.” The level of statistical significance is indicated as control vs. induction ($P < 0.0001$)

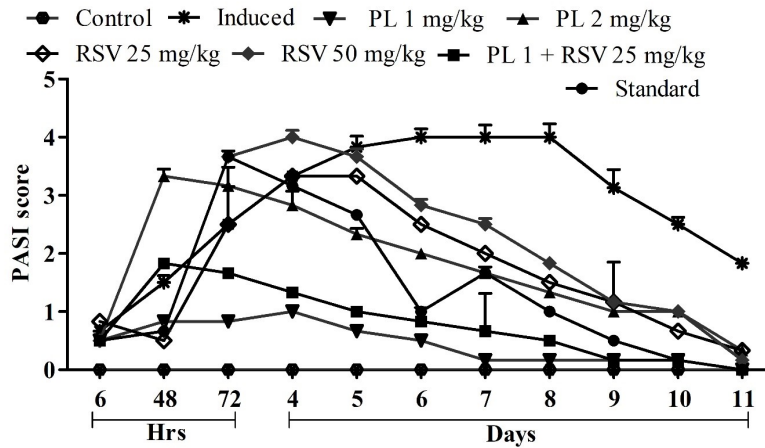


Figure 2. Effect of PL and RSV alone and in combination on psoriasis-like conditions in rats. “The values on the graph for the respective groups (n=6) are represented as mean ± SEM and data was analysed by “two-way ANOVA followed by the post hoc Bonferroni’s multiple comparison test.” The levels of statistical significance were as follows: control vs. induction (P<0.0001), PL (1 mg/kg- 72 h P<0.001), PL 2 mg/kg (48 h onward, P < 0.001), RSV 25 mg/kg (day 6 onward, P<0.001), 50 mg/kg (48 h onward, P<0.001), and PL 1 mg/kg + RSV 25 mg/kg (72 h onward, P<0.0001) versus induction group

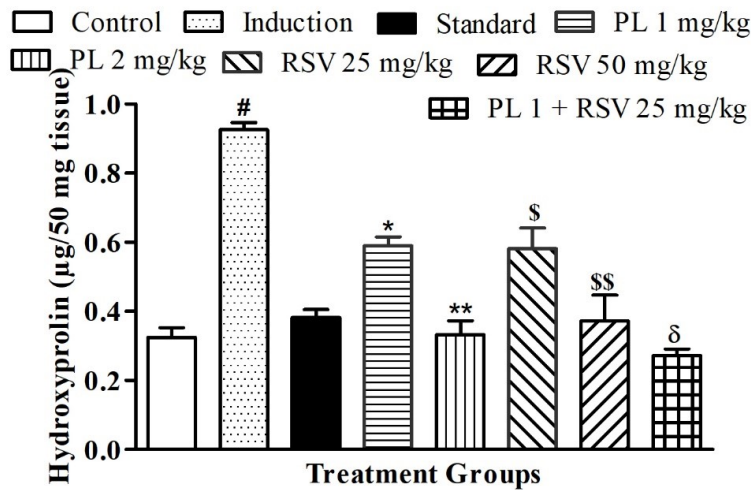


Figure 3. Effects of PL and RSV on HP content in psoriasis-like condition-induced rats. “The values on the graph for the respective groups (n=6) are represented as mean ± SEM and data was analysed by “one-way ANOVA followed by Bonferroni’s multiple comparison test”. The level of significance is expressed as #P<0.0001 versus control, *P<0.001, and **,SS,δ P<0.0001 versus the induction group

3.3. Effect of PL and RSV on the HP Content in Psoriasis-Like Condition-Induced Rats

As shown in Fig. 3, UV radiation caused skin tissue damage and significantly elevated (one-way ANOVA, P<0.0001, $F_{7, 47} = 27.49$) the HP content as a marker of the psoriasis-like condition as compared with the group of control rats. In contrast, treatment with the standard, PL (1 & 2 mg/kg), RSV (25 & 50 mg/kg), and PL 1 mg/kg + RSV 25 mg/kg significantly restricted the elevation of HP content compared to the induction group. Higher doses of PL and RSV were indicative of complete reversal, and the combination of lower doses showed synergistic interactions. No significant differences were evident among the control, standard, PL 2 mg/kg, RSV 50 mg/kg, and PL+RSV combination groups.

3.4. Effect of PL and RSV on Histopathology of Psoriasis-Induced Rats

As shown in Fig. 4, the microscopic data for the induction group revealed a significant increase in scaliness, keratinocytes, and epidermal thickness in the basal layer, indicating hyperproliferation and acanthosis. In addition, lymphocyte infiltration, rete ridge elongation, and micro-abscesses were observed. In contrast, PL 2 & RSV 50 mg/kg, standard cream, and the PL+RSV combination reduced inflammatory changes, keratosis, and thickness with no or less rete ridge formation.

3.5. Binding Interaction of PL and RSV with Various Receptor Protein

PDB for mammalian targets of rapamycin (mTOR),

fibro-collagenase, and nuclear factor kappa B (NF κ B) were screened based on resolution, unique ligands, mutational status, and outliers (Table 1). PL and RSV showed aggregable affinity and binding interactions with mTOR,

fibro-collagenase, and NF- κ B. RSV has proven to be a better fit than PL as a ligand for the respective receptor protein, which could be a possible target of their action (Fig. 5).

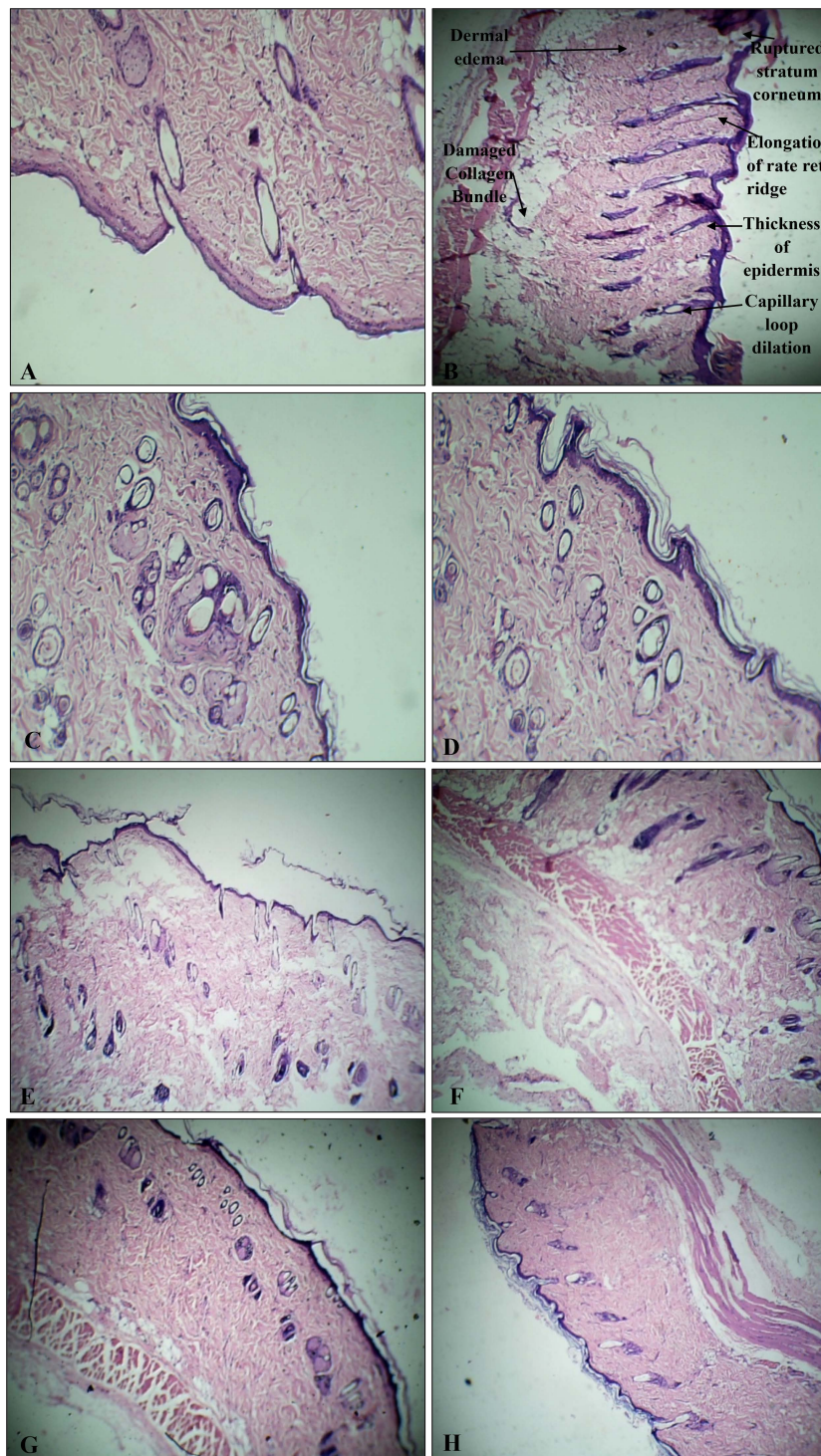
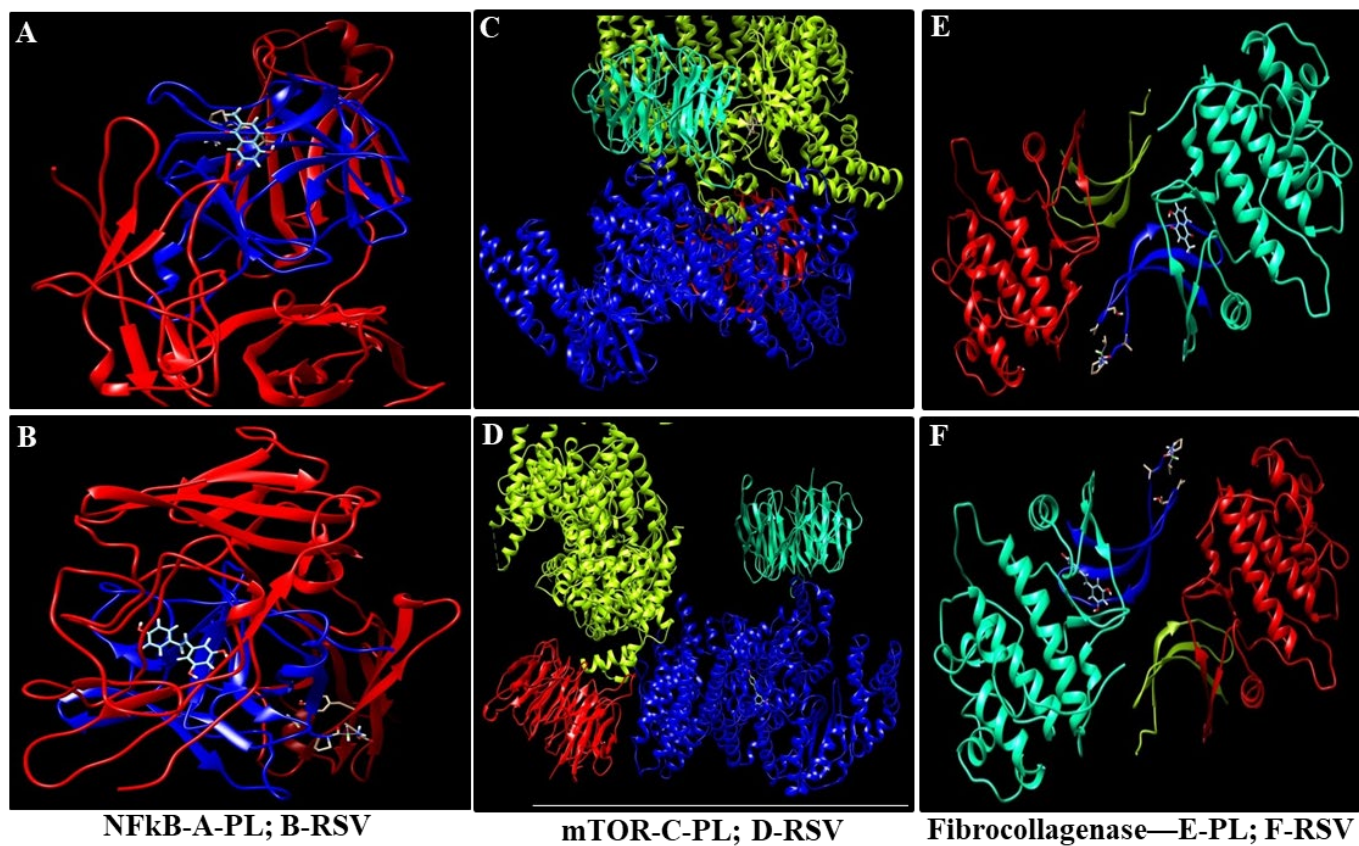


Figure 4. Histopathological examination of rat skin in UV-induced psoriasis. “A. Control normal skin architecture; B. Induction, hyperproliferation, rete ridge elongation, damaged stratum corneum, lymphocytic infiltration, epidermal thickness, capillary dilation; C. PL 1 mg/kg, D. PL 2 mg/kg; E. RSV 25 mg/kg; F. RSV 50 mg/kg; G. PL+RSV; H. Standard”

Table 1. In silico interaction of PL and RSV with various target protein

Target	PDB	Resolution	Mutation	Unique Ligand	Complexed with /Inhibitor	PL	RSV	Chain	STD	Standard
mTOR	4JSN	3.2	No	NO	Ser thre Ptot Kin mTOR	-6.90	-7.90	B-1385-24; D-8-308; A-1385-2435; C-8-308		Sirolimus
Fibrocollagenase	2TCL	2.2	NO	CA, RO4, SM, ZN	WI-Unknown	-6.00	-6.63	1-163	-6.50	Zin
NFkB	4Q3J	1.86	NO	MG, ZN	NO	-6.09	-7.38	A (22-272)	-9.82	Sutinib

**Figure 5.** In silico interactions of PL and RSV with receptor proteins. A. NFkB; B. mTOR, C. Fibro-collagenase

4. Discussion

Psoriasis is a progressive inflammatory and autoimmune condition associated with multifactor-mediated signalling pathology [2], [28]. UV light exposure for 15, 30, and 45 minutes has been reported to induce psoriasis in rodents and is established as an induction model for preclinical psoriasis-like conditions [21]. The degradation of collagen and liberation of HP exposure to UV light radiation as a result of natural aging, contribute to psoriasis [11], [29]. Researchers have reported the potential benefits of restoring or regenerating collagen levels in the treatment of epidermal damage and psoriasis-like conditions [21], [30]. The immune cell infiltration, hyperproliferation, and disrupted keratinocyte differentiation result in epidermal thickening and scaling. This results in significant lesions, and rete ridge formation contributes to psoriasis [3]. The UV radiation exposure caused disruption of the epidermis, rete ridge elongation, leucocytic infiltration, and capillary dilation in the induction group animals. PL and RSV reduced the suffering of UV-exposed rats, alleviated macroscopic changes in skin structure, and expedited the recovery, i.e., within a week. Histopathological data revealed that PL and RSV reduced inflammatory changes, keratosis, and epidermal thickness, with no or less rete ridge formation. The suppression of inflammatory processes linked to psoriasis has demonstrated efficacy as a therapeutic approach for psoriasis management [15].

Current psoriatic treatment includes the use of salicylic acid, corticosteroid, coal tar, immunosuppressant, vitamins i.e. A, D, and E [17], [31], [32], [33]. Their anti-psoriatic regimen is multifaceted and has some drawbacks, including temporary discoloration, irritation, redness, and burning. As a result, psoriasis has traditionally been treated with several plant-based medicines [19], [34]. Salicylic acid exhibits analgesic as well as anti-inflammatory properties, but on continuous use produces salicylism as an adverse consequence [12]. According to Shalaby et al. [15], the use of a fixed-dose combination including corticosteroids and salicylic acid, specifically Diprosalic and Nerisalic, exhibits greater potential as an anti-psoriatic treatment compared to the use of a single drug. Due to their cost-effectivity, accessibility, enhanced tolerance, decreased side effects, good protection, and optimum efficacy various herbal formulations may be established as alternatives to allopathic medications [2], [3], [34]. Literature reported that curcumin, RSV, vitamin D & E, fatty acids (omega-3), and gallic acid can be established as promising therapies for psoriasis [5], [32]. Hence phytoconstituents like RSV a phytoalexin and PL a naphthoquinone with anti-inflammatory antioxidant potential were used [35].

In psoriasis, activation of T cells is mediated through macrophages via $TNF\alpha$, IL-6, IL-23, and IL-1 β production, while RSV has been found to decrease the macrophage infiltration and proinflammatory levels in vivo and in vitro

[17], [36], [37]. RSV activates SIRT1, abolishes IL-17a and 19 mRNA expression, regulates aquaporin (AQP)-3, and reduces keratinocyte proliferation [38], [39]. The dose translation of RSV from animal to human can be easy, based on the body's surface and it is available as a cost-effective food supplement [40]. RSV has been proven as a safe and efficacious polyphenolic nutraceutical in more than 250 clinical trials for its pleiotropic properties, including its anti-inflammatory activity [36], [41]. It greatly impacts chronic inflammation, oxidative stress parameters, and related microRNA expression in diabetic patients [42], [43]. According to Elgewelly et al. [44], 0.1% RSV-loaded spanlastic gel demonstrated an anti-psoriatic effect through modulation of inflammatory cytokine proliferation.

Plumbago Zeylanica extract ameliorates the epidermal thickness through the cell cycle and apoptosis and also prevents the mRNA expression and IL-23 serum level [29]. PL has been found to alleviate carrageenan-triggered inflammation through the inhibition of cyclooxygenase (COX)-2 and proinflammatory cytokine production [38]. The cytotoxicity, physical instability, solubility, and oral bioavailability (<40%) are some challenges during its clinical exploration. These limitations can be overcome by using specific investigations and preparing novel formulations like liposomes, microspheres, nanoparticles, micelles, and metal nanoparticles [31], [45], [46]. In our previous work, PL and RSV exhibited synergistic anti-inflammatory and analgesic properties through their antioxidant and inflammatory mediators' modulatory mechanisms possibly via superoxide dismutase (SOD), glutathione (GSH), IL-6, and COX2 interactions [35].

Present research supports the above findings; UV exposure induced psoriasis-like conditions in 30 minutes and was established as the optimum time duration for psoriasis induction. Treatment with PL (2 mg/kg) and RSV (50 mg/kg) alone decreased the PASI score, restored the HP content, and enhanced healing. The sub-effective dose combination of PL and RSV showed synergism, which was equivalent to the effect of a higher dose of PL and better than the standard treatment. PL has been proven to be better at higher doses but its sub-effective combination with RSV reduced the dose and ensured its safety limitation.

Targeting mammalian targets of rapamycin (mTOR), NF κ B, and COX2 is crucial for psoriasis therapy [9], [47], [48]. Matrix metalloproteases like collagenase are important for the pathologic restoration of skin during pathologic conditions like psoriasis [49]. The docking study supports the in vivo data and predicts that the interaction of PL and RSV with important targets like mTOR, NF κ B, and fibro-collagenase indicates their multi-target modulatory potential.

Both the drugs might have modulated macrophage infiltration, COX2, oxidative parameters, IL-1, 1 β , 6, and 23, while RSV could have additionally inhibited IL-17a,

IL-19, and SIRT1 activity that may contribute to their synergistic anti-psoriatic effect. Thus, in vivo, in vitro, and in-silico data support the anti-inflammatory and multi-target modulatory effects that may be involved in the anti-psoriatic mechanism of the PL and RSV.

5. Conclusions

The UV model used for psoriasis induction has successfully mimicked the psoriasis-like condition in rats. The PL and RSV alone have proven to be significantly effective, and their sub-effective combination is potentially synergistic in the PASI score reduction, HP, histopathological, and macroscopic character restoration. The PL and RSV being anti-inflammatory could have inhibited macrophage infiltration, proinflammatory cytokine, and keratinocyte production. In addition, NFkB, fibro-collagenase, and mTOR may be involved in the anti-psoriatic mechanisms of PL and RSV.

Further investigation is required to find out the molecular and genetic aspects, formulation of a suitable dosage form, and clinical investigation for commercialization of the product.

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Conflict of Interest

No conflict of interest associated with this work.

Authors Contribution

Conceptualization and methodology, writing-original draft preparation, data analysis, interpretation, and in-silico docking-PNA, Investigation-PNA, RPS; Supervision, SAD. All authors have read, agreed, and approved the final version of the manuscript.

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