Int J Ayurvedic Med,Vol 17 (1), 2026; 185-197

Ayurveda Sahiti Prabha's

International Journal of Ayurvedic Medicine

ISSN No: 0976-5921

Research Article

Formulation and pharmacological evaluation of anti-psoriatic gel of *Rivea hypocrateriformis (Desr.)* Choisy

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Received: 20-01-2025 Accepted: 19-02-2026 Published: 31-03-2026

Abstract

Psoriasis is an auto-immune disease, which is characterized by dry skin and red patches all over the body and shedding resembling fish scales. The skin disease is accompanied by an Atopic type of dermatitis then eczema that may finally lead to a psoriatic condition. *Rivea hypocrateriformis* in Tamil is named as Bhodhi Keerai or Musutai Kodi. Among the aerial parts leafy portion was taken and dried in shade, coarsely powdered, and further research was carried out. Ethanolic extracts of leaves were prioritized for the research. Anatomical characters of leaves reveals the presence of Palisade, collenchyma, spongy parenchymatous cell with starch grains in entire mesophyll regions.Appressed covering trichomes are found in the upper and lower parts of the epidermis with the Paracytic type of stomata with aimed to correlate all the studies.*Rivea hypocrateriformis* reveals the presence of active constituents such as Phloretin, Hexadecanoic acid Rutinoside by GC-MS analysis,then by means of *In silico* screening it proves that Rutin binds with the protein IL2 and TNF alpha which exhibits the therapeutic benefits in curing skin diseases, anti-inflammation, anti-oxidant ,anti- cancer and various disease ailments.DNA barcoding performed for this species and compard with *Rivea ornata and Rivea clarekinata* by means of which the genes were authenticated and the species *Rivea hypocrateriformis* was identified. Gel was formulated with ethanolic leaf extract of *Rivea hypocrateriformis,*The *Rivea hypocrateriformis* gel at 100µg/mL substantially inhibits inducible nitric oxide synthetase enzyme and other inflammatory mediators which are responsible for swelling. Imiquimod-induced psoriatic activity in rats was performed with the *Rivea hypocrateriformis* gel in curing mild Atopic to severe psoriatic skin diseases.The regeneration of skin were examined which gives a prompt response at 400mg/kg of *Rivea hypocrateriformis* gel compared to 1% Salicylic acid, by declining the effects of Erythema, Induration, and Desquamation.

Keywords: Carbopal, Propylene Glycol, Frans Diffusion Cell membrane, 5% Imiquimod cream, *Rivea hypocrateriformis* extract, 1% Salicylic acid.

Access this article online

Website: https://ijam.co.in

DOI: https://doi.org/10.47552/ijam.v17i1.6559

Introduction

Psoriasis is described as a noncontagious autoimmune disease that can be characterized by reddish, pink, itchy, and scaly patches with abnormal skin. It varies similarly like small patches and slowly spreads across the entire body. Psoriasis occurs due to a weaker immune system and induces the production of cytokines mediators. In the human body, numerous skin cells grow and fall off within a month, but in patients with psoriatic conditions, their skin cells grow and pile up in the form of plaque despite shedding down. This leads to inflammation and causes painful lesions in the affected area.

In a year of about 6 million ago, United States have been affected with this eczema-like symptoms, are most common in both males and females. It may appear at any age group including the Infant stage. The common sites where psoriasis occurs accompany certain regions like scalp, elbow, knees, and any part of the groin region of skin may also be affected. Psoriasis severity increases in certain patients due to continuous scratching and that deals with lichen formation, when the psoriasis plaques disappear it may leave brown or pale black marks that may take several months to cure.

Psoriasis is determined by the Koebner phenomenon which explains the appearance of lesions in psoriatic affected regions due to itching, injury, or burning. It is a recurrent and debilitating

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disease. The symptoms of Psoriasis may vary from one individual to another it resembles like Atopic type of Dermatitis and remains the same throughout the year then slowly if not treated it may lead to bleeding in the skin with white silvery patches. Improper diet, weather conditions, stress, and environmental changes are some of the factors to cause Psoriasis.(1-8)

Materials and Methods

Rivea hypocrateriformis (Desr.) Choisy specimen was confirmed by a Taxonomist at Xaviers College in Tirunelveli District. After being cleaned and allowed to dry in the shade, the leaves have been employed in the ensuing research. The two major steps involve extraction of Genomic DNA, PCR amplification, and sequencing and Phylogenetic analysis and *Rivea hypocrateriformis* (sequencing)

Employing the CTAB (Cetyl trimethyl ammonium bromide) buffer technique, the genomic DNA of the obtained raw drug samples had been isolated. 100mg of the samples were ground with 400-500µL of CTAB buffer (10ml 1M Tris-HCL base with pH 8, 8ml of 0.5M Ethylene diamine tetra acetic acid, 28mL Sodium chloride,40mL water, 2gms (CTAB) using mortar and pestle, the entire mixture is being transferred to the 2ML Eppendorf tube then extracted the tissues by added more 500-600 µL of CTAB extraction buffer to make it up to 1mL and pinch of PVP (polyvinylpyrrolidone) plus70-80µL 1% of β-mercapto ethanol.

After the mixture had been well mixed, it was incubated for 45 minutes at 65°C in a water bath. Once completion of incubation, the products were kept for cooling down to room temperature, and 60µL of chloroform: Isoamyl alcohol and mixed by lightly inverting it for few times. The tubes were kept for centrifugation at 10,000 rpm for 3min and the clear liquid would be seen at the top, that supernatant was transferred into new tubes, add 500µL Phenol: Chloroform: Isoamyl alcohol and again the centrifugation was repeated. Lastly cold isopropanol was added to the supernatant and inverted gently to mix it, once again it undergoes centrifugation at 10,000 rpm; 3 min and 4°C after the centrifugation DNA crystals in form of pellet visible at the bottom.

The supernatant liquid was separated and the sample settled at the bottom(pellet) was rinsed with alcohol. The pellet obtained dried at room temperature for 12hrs. until it dried completely at normal temperature, then resuspended in 100µL of sterile water. The DNA was inspected with 0.8 % agarose gel. The mixture includes template, buffer, dNTP, primer, polymerase, DMSO and sterile water. The entire RBCL gene is expatiated from genomic DNA by means of thermocycler programme with a denaturation step carried on, accompanied for 32 days by maintaining an appropriate temperature and time from 50°C to 94°C for 60 seconds and extending at a certain limit frame, for protraction step. ITS2 spacer amplification products were sequenced. Neighbour-joining analysis was performed for the above dataset in Geneious Pro using HKY model (Kasegawa-Kishino-Yano). No outgroup was selected since the tree topology has been expected to understand the genetic relatedness and the placement of *Rivea* species along with other entities that are archived from NCBI mentioned in Figure 1 (10-16)

GC-MS Analysis of *Rivea hypocrateriformis*

The design and intent of GC-MS are to examine the Phytochemical substances found in a crude ethanolic extract of *Rivea hypocrateriformis* leaves. The peaks seen at both low and high molecular weights in the analysis by GC-MS signify the existence of 21 phytochemical compounds revealed in Fig 2 & Table 1. These phytoconstituents reveal the various therapeutic benefits. The following are the Parameters used are given below (17-30)

- Column oven temperature - 50.0°C
- Injection Temperature-250.00°C
- Injection Mode-split
- Flow control mode-Linear velocity
- Pressure-68.1Pa
- Total flow-16.2mL/min
- Column flow-1.20mL/min
- Linear velocity-39.7cm
- Purge Flow-3.0mL/min
- Split Ratio-10.0

Molecular docking of Rutin

The stability as well as interactions of the optimum binding complex, comprising ligands along with proteins, have been evaluated utilizing Schrodinger with Desmond simulation tools. The modules for grid creation, Ligprep, protein preparation, as well as glide docking have been utilized to examine the molecular mechanics interaction of the rutin phytoconstituent with IL-2 (1M48) & TNF-α (7JRA) proteins. The dynamic simulation, system builder, simulation interaction, as well as simulation quality diagram modules, have been applied to perform quantum mechanics-based stability analyses of the complex.

To investigate the interaction between IL-2 (1M48) and TNF-α (7JRA) proteins, rutin is synthesized as a "stable molecule at a local energy minimum level. The pdb file serves as input in the protocol preparation. Protein preprocessing involves assigning bond orders utilizing the CCD database in addition to replacing hydrogens. Based on zero-order Metal and disulfide bonds are created. To generate pH states set at 7.0 ± 2.0 Epik module is employed. The pre-processed protein is further subjected to optimal hydrogen bond assignment with the PROPKA optimization approach, accompanied by sample water orientation. The protein has been reduced by employing a heavy atom RMSD of 0.30 Å via the OPLS4 force field calculation. The molecules of water located beyond 5 Å from the PDB ligand have been eliminated. Rutin is produced for docking with the LigPrep technique. The method employs OPLS4 force field parameters with Epik, while the system" has undergone desalination. Ligand molecules with various stereoisomers have been produced.

The grid receptor generation procedure is obtained with the PDB ligand site inside a PDB protein IL-2 (1M48) and TNF-α (7JRA) as a binding pocket for rutin phytoconstituents. The scaling factor, aligned with the Van der Waals radius, had been established at 1.0 Å, accompanied by a partial charge threshold of 0.25. The dock ligand length is set to 12 Å, while the enclosing box was adjusted to fit at the centroid of the workspace ligand. A partial charge cutoff (Van der Waals radii) of 0.15 with a scaling factor of 0.80 has been employed for developing the ligand docking approach. Upon loading the grid file, a flexible ligand sampling configuration was employed in conjunction with the XP additional precision method. To bias samples of torsion, nitrogen inversion samples, ring conformations, along with all predefined functional groups have been applied.

The final docking score is inflated by the Epik state penalties. A conformer creation is maintained by minimising the distance-

dependent dielectric constant value set at 2.0, and the ring sampling energy window was set at 2.5 kcal/mol. For the superior poses of salicylic acid & rutin, the Prime-MMGBSA procedure additionally served to investigate the binding energies with the TNF-α (7JRA) & IL-2 (1M48) proteins. VSGB has been employed as the solvated model as well as OPLS4 as the force field protocol. Further, Phe A:42 formed two π-π bonds by interacting with chromone-based derivative ring of rutin. Additionally, some hydrophobic amino acids such as Leu B:105, Ala B:109, Ala B:111, Ala A:73, and Leu A:72, aid the rutin molecule to properly orient inside the binding cavity. The standard salicylic acid only forms one hydrogen bond with Arg A:38, and the salt bridge is generated with ionized carboxylic acid are mentioned in Fig 3,4,5&6 & Table 2.(31-40)

Gel of *Rivea hypocrateriformis leaf extract*

The leaf extract of *Rivea hypocrateriformis* is mixed with Carbopol 934, propylene glycol, glycerine, and Triethanol amine at different concentrations of extracts to incorporate into a gel formulation. The gelling agent used to obtain the desired texture, stability, and release of active ingredient, to dissolve the plant constituent's suitable vehicle has been used. Preservatives are used to ensure and maintain stability and prevent contamination. pH should be optimized throughout the preparation for skin compatibility and tabulated in Table 3.(41-50)

***In vitro* Drug Diffusion Study**

Sigma Chemicals provided the cellophane membranes employed in the research. A donor compartment containing 1.0 gm of gel was maintained in a Kiescary Chien (KC) diffusion cell. All of the membrane's exposed surface was immersed in the 0.1 N NaOH solution present in the receptor compartment's 85 ml volume. A magnetic stirrer was used to maintain constant stirring (100 rpm) in the receptor compartment at 37.1°C. After a day, the sample was replaced with the same volume of brand-new 0.1N NaOH after measurements were made at 1,2,4,6,8,10, and 24-hour intervals. At 392 nm, the absorbance of the sample had been measured following parameters shown in Table 4&5 in Figure 7

Drug Release Kinetic Study

The following equations were used to fit the release data and examine the topical gel's drug-release mechanism:

Zero – order

Q = k0t, where k0 is the zero-order rate of drug release, at any time t.

First–order: $\ln(100 - Q) = \ln 100 - k1t$

Where, k1 is the first-order release Q is the percentage of drugs released at time t.

Higuchi's: $Q = k2\sqrt{t}$

Where k2 is represented by the Diffusion rate constant and drug release percentage Q at time t.

Rheological studies

The Brookfield LVDV-E type viscometer was used to take the readings. The sampling tube now contains the gel formulations. Before each measurement, the product was retained in a circulating water bath using the viscometer adapter. The formulation's viscosity was determined by increasing the spindle's angular velocity from 1 to 4 and also were described at Table 6.

Spreadability study of Topical gel

Spreadability was then calculated using the following formula:

$$S = M \times L / T$$

Where, S = is the Spreadability, M = is the weight of the pan (tied to the upper slide), L = is the length moved by the glass slide and T = represents the time taken to separate the slide from each other as mentioned

Imiquimod-induced psoriatic-model in rats

Animals were approved as per CPCSEA guidelines by the Animal Ethical Committee with the following Reference No/CLATR/IAEC/XX/196/2022. Eight- to eleven-week-old rats were employed in the research. Animals were trapped in cages and given back shaves in each of the groups used in the experiment (healthy, control, and diseased). Rats were given a total of 62.5 mg of imiquimod topically over 7 consecutive days; this works out to 3.125 mg of the active ingredient each day. After taking away the hair from the animal's back, 5% Imiquimod cream (Aldara;3 M Pharmaceuticals) was applied. The rats in the control group were treated the same way, except they were given a vehicle cream. The skin was collected on the 7th day and then located in the formalin solution. A piece of tissue was cut at 4 micrometres and produced a spot with hematoxylin and eosin reagents. The tissue degeneration has been evaluated employing a Nikon trinocular microscope, model E-200.(50-71)

Acute skin irritation test

An acute skin irritation test has been performed. A healthy young female rat between 8 and 12 weeks was employed for this study. Animals were confined in cages for a minimum of five days before the experiment. Before starting the experiment, the animals had been fasted overnight and allowed free access to water *ad libitum. Rivea hypocrateriformis* gel of 400mg/kg was applied externally (As per OECD Guideline 404). Three animals were used for each set of experiments. Animals were treated with mid and low doses. All the test animals were observed for 14 days and subsequent parameters were determined Mortality, salivations, changes in skin color, and lesions or wounds were tabulated in Table 9,10,11.

Scoring severity of skin inflammation

Histopathological analysis and PASI (Psoriatic Area and Severity Index) ratings (zero, mild, moderate, and severe) were used to arbitrate the efficaciousness of *Rivea hypocrateriformis* plant-based gel for the therapy of psoriasis. The dorsal skin showed indications of erythematous scaling and dermal thickness from two or three days after IMQ (Imiquimod) administration began. once therapy began, the severity of the afflicted mice's psoriasis-like symptoms worsened steadily until day 14.

- Dose fixation as per OECD guideline 423
- Group I- Control treated daily with Vaseline showed no symptoms of irritation.
- Group-II-Imiquimod-induced rats with 1% salicylic acid
- Group-III- *Rivea hypocrateriformis* gel 100mg/kg of body weight
- Group-IV- *Rivea hypocrateriformis* gel 200mg/kg of body weight
- Group-V- *Rivea hypocrateriformis* gel 400mg/kg of body weight
- PASI=Head+Arms+Trunk+Legs=D Score

- Psoriasis is indicated by score method 0-72% range to score 6 whereas 1-9% range to score 1

Group I (Normal control group)

Wistar rats were chosen in this group Vaseline was used as a control which reveals no symptoms of irritation.

Group II (5% Imiquimod cream)

Animals were treated with Imiquimod cream 5% it is a steroid that continuous use leads to Atopic type of dermatitis and Psoriasis. After induction slowly the red spots, thickness & keratosis appeared on the 7th day and that was treated with salicylic acid 1%. By the completion of the 14th day, the animals had been sacrificed for histological analysis.

Group III (*Rivea hypocrateriformis* gel 100mg/kg)

Animals treated with *Rivea hypocrateriformis* gel 100mg/kg shows still the presence of red spots, thickness, and dry skin. The animals had been ultimately sacrificed for histological analysis.

Group IV (*Rivea hypocrateriformis* gel 200mg/kg)

Animals treated with *Rivea hypocrateriformis* gel 200mg/kg shows still the presence of red spots, thickness. The animals had been ultimately sacrificed for histological analysis.

Group V (*Rivea hypocrateriformis* gel 400mg/kg)

Animals treated with *Rivea hypocrateriformis* gel 400mg/kg shows absence of red spots and growth of new hairs. The animals had been ultimately sacrificed for histological analysis.

Two or three days into IMQ treatment, the dorsal surface of the skin displayed signs of erythematous, fishy scales, and redness of the skin. Psoriasis severity symptoms in Wistar rats continuously increased. Wistar rats in Group I that received a daily placebo drug on their dorsal skin had no signs of skin irritation. After applying Imiquimod, inflammation levels increased steadily from day 1 to day 7, as measured by separate PASI scores, until therapy with salicylic acid 1%, Herbal extract gel of *Rivea hypocrateriformis* was begun. Psoriasis-like dermatitis was successfully induced in the IMQ-treated rat, as shown by the highest intensity of PASI scores on day seven following treatment. However, psoriasis-like symptoms decreased significantly starting on day 8, only two days after therapy with Salicylic acid 1% (group II) and *Rivea hypocrateriformis* gel extract (groups III, IV, V) was started. The PASI scores for each group, as well as the average score for days 1-14, are shown. When compared to the Imiquimod-treated group, *Rivea hypocrateriformis* gel extract considerably reduced the severity of the psoriasis-like dermatitis caused by IMQ. PASI inflammatory symptoms reduced with plant-based gel extracts of 400 mg/kg plant gel compared with 100 mg/kg of plant-based gel extract were determined in Figure 8,9,10 &11.

Histopathological Studies

Histopathological studies determine the degenerative change in the epidermis, an increase in keratin formation a decrease in the percentage of orthokeratosis zones, an extension of rete ridges, the dilation of the capillary loops, and the presence of a minimal grade lesion of Munro's micro abscess are all indicative of severe tissue damage in imiquimod-treated skin samples, as shown by histological analysis. Animals administered Salicylic acid and *Rivea hypocrateriformis* gel extracts showed signs of normal skin cytoarchitecture, suggesting the presence of regeneration mechanisms and mentioned in Figure 12.

Result

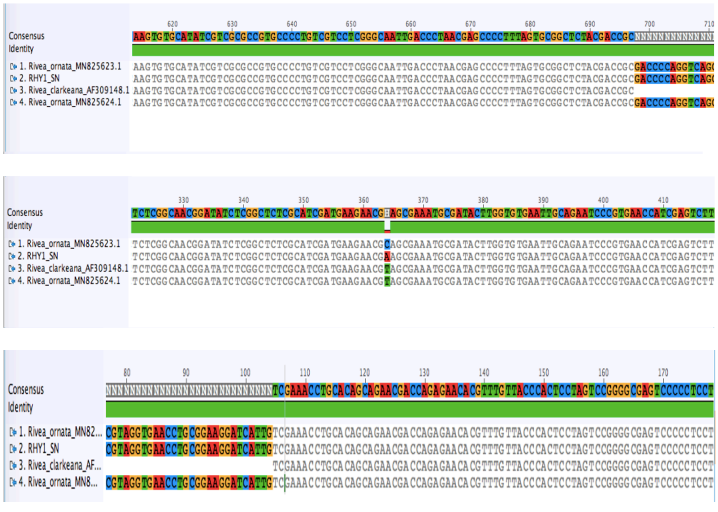
DNA Bar coding *Rivea hypocrateriformis*

In this context the DNA based molecular marker technique provide a platform for the authentication of various parts of plant species which includes bark, leaves, root, seed etc. The Genes of *Rivea hypocrateriformis* is compared with the genes of various species such as *Rivea ornate* and *Rivea Cordifolia* from different places,it was confirmed and authenticated as *Rivea* species.The following genetic characters of the species are listed below. DNA markers have been employed for identification of rare medicinal plant species while establishing a reference library for traditional medicine. Among the variety of DNA markers, SCAR, LAMP, as well as DNA barcoding considered optimal for authentication.

Isolated DNA from the young leaves of *Rivea hypocrateriformis* was identified by RAPD (Rapid amplified polymorphic DNA) markers, this method is employed for the genetic, taxonomic, and polygenic mapping of species. Using Polymerase chain reaction DNA barcoding was obtained clearly, the unique appearance of bands determines the Genuity of the species. By mapping the genes with other species of *Rivea* the DNA profile of the plant was authenticated. The above findings with marker genes prove to be effective in identifying the plant species. It also provides information to distinguish from other related species. The accuracy of plant species can be justified by this gene comparison method.

GTCCACTGAACCTTATCATTTAGAGGAAGGAGAAGTCGTAAC
AAGGTTTCCGTAGGTGAACCTGCGGAAGGATCATTGTCGAAA
CCTGCACAGCAGAACGACCAGAGAACACGTTTGTTACCCACT
CCTAGTCCGGGGCGAGTCCCCCTCCTCGGGGGAGGGCTGGCC
TCGGCCGAACAACGAACCCCCGGCGCGGAACGCGCCAAGGA
ATACTAAAATGAGATGGCCAGCCGCCCATGCACCGTTATTGCG
GACCGTGCGGGAGGTGTAGGTGTCTTGATTAATAAAAAACGA
CTCTCGGCAACGGATATCTCGGCTCTCGCATCGATGAAGAAC
GAAGCGAAATGCGATACTTGGTGTGAATTGCAGAATCCCGTG
AACCATCGAGTCTTTGAACGCAAGTTGCGCCCGAAGCCGTCA
GGCCGAGGGCACGTCTGCCTGGGCGTCACGCATCGCGTCGTC
CCCCTACTCTATGCTTAGTAGAGCAAGGGGGAGCGGATGATG
GCCTCCCGTGCCCCCACTAGGGGCGTGGTTGGCCCAAACGCG
AGTCCTTGGCGACGGACGTCGCGGCGAGTGGTGGTCGTACC
AAGTGTGCATATCGTCGCGCCGTGCCCCTGTCGTCCTCGGGC
AATTGACCCTAACGAGCCCCTTTAGTGCGGCTCACGACCGCG
ACCCCAGGTCAGGCGGGATTACCCGCTGAGTTTAAGCATATC

Figure 1 Comparison of genes with *Rivea* species



GC-MS analysis of *Rivea hypocrateriformis*

GC-MS confirms the presence of 20 compounds were identified such as phloretin, hexadecenoic acid, and histeridine; these compounds are used to cure certain skin diseases and act as Analgesic and anti-inflammatory.

These compounds identified in *Rivea* species can be isolated for their therapeutic benefit which by means it potentiates its utility for future research work.

The chromatogram obtained exhibits each peak which represents volatile compounds present, and also previous studies in LC-MS analysis of leaves of *Rivea* species reported 21 compounds, this gives valuable information for isolating secondary metabolite.

Figure 2: GC-MS Analysis of *Rivea hypocrateriformis*

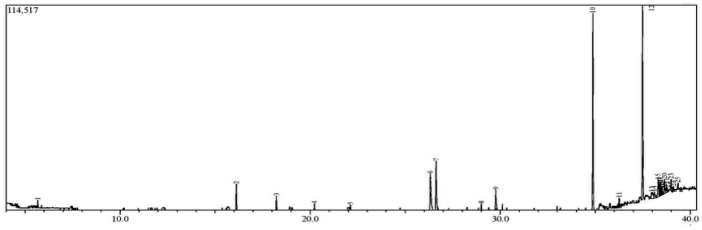


Table 1: Phytochemical compounds of *Rivea hypocrateriformis* Leaves

S. No	Chemical name	Chemical formula	Weight	Peak percentage	Retention factor
1	Di-iso decyl phthalate	C28H46O4	446	37.491	27.16
2	1,4-Benzene dicarboxylic acid, bis(2-ethylhexyl) ester	C20H26O4	330	37.491	27.16
3	Phthalic acid (2-propyl pentyl) ester	C24H38O4	390	34.875	25.81
4	Benzoate 3-amino-5 hydroxy-Methyl ester	$C_8H_9NO_3$	167	26.319	7.73
5	Hexadecanoic acid	C16H32O2	256	26.621	7.48
6	Pentadecane	C15H32	212	16.122	3.14
7	Penta chloro bromo benzene	C_6Brcl	326	29.762	2.83
8	4-isoxazolamine,5-(1-methylethyl)-n-[(1-ethyl) carbon Imidoyl]	C10H15N30	193	38.641	2.56
9	(E,E)-2[3(Dimethylamino)-2-propylidene] cycloheptanone	C12H19NO	193	37.963	2.21
10	(+-)-1-(acetoxy)-2-(1-bromoethyl)-3-methoxy anthraquinone	$C_{19}H_{15}BrO_5$	402	37.963	2.21
11	Butyl 4,4-difluoro-3-butenoate	C8H12F2O2	178	38.985	1.74
12	2,2'-methylene-bis(4-methyl-6-tert-octylphenol)	C31H48O2	452	36.248	1.46
13	Ethyl 2-chloro-3,3,3-trifluoro-2-methoxy-propeonate	$C_6H_8C_lF_3O_3$	220	36.248	1.46
14	Phthalic acid, cyclobutyl tridecyl ester	C25H38O4	402	38.105	1.34
15	3,3-bis(trifluoromethyl)-2-thiabicyclo [2.2.1] hept-5-en-2,2-dioxide	$C_8H_6F_6O_2S$	280	38.747	1.24
16	3-Rutinoside	C27H30O15	610.15	448.87	0.16
17	Di hydroprotolic hesterinic acid	C19H34O4	326	38.385	0.99
18	1-butene,3,4-dibromo-2-methyl-Phloretin	C15H14O5Br2	226	39.101	0.98
19	5H-Tetrazol-5-amine	CH_3N_5	85	5.673	0.72
20	Di sulphide Dioctyl	C16H34S2	290	20.227	0.6
21	2-Propenamide	C_3H_5NO	71	29.003	0.59

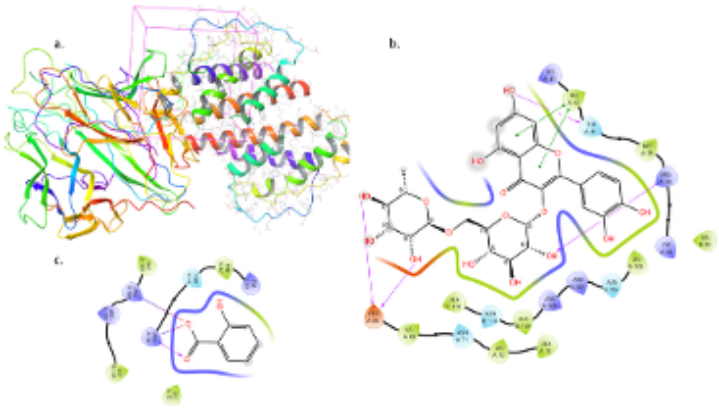
Docking studies

Binding of rutin and salicylic acid molecule with the protein 7JRA showed the formation of appropriate conformation inside with a higher affinity of -71.58 kcal/mol compared with standard 42.02 kcal/mol.(45-47)

Table 2: Dock score and MMGBSA energy of 1M48 & 7JRA protein

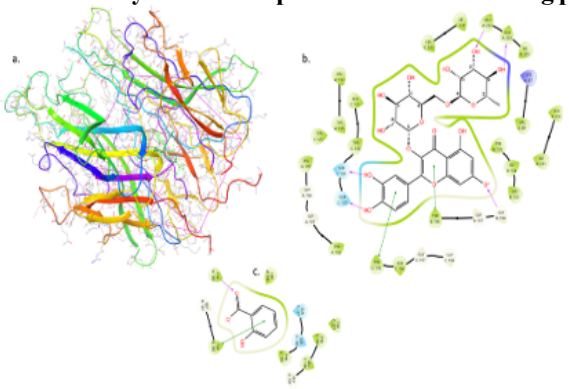
Ligand	Docking Energy of	Mmgbsa Energy
1M48		
Rutin	-5.485	-41.58
Salicylic acid	-3.973	-16.91
7JRA		
Rutin	-10.841	-71.58
Salicylic acid	-6.326	-42.02

Figure 3: Secondary structure of protein1M48 with binding pocket



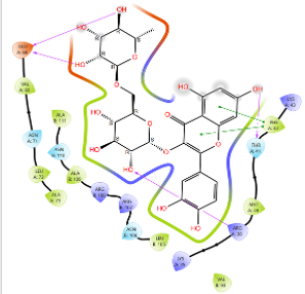
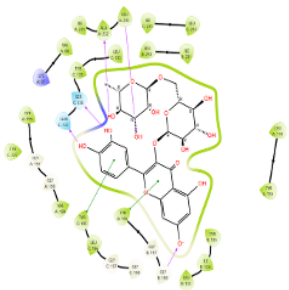
Rutin binding pocket with active site amino acids. Salicylic acid interaction inside the binding pocket. It illustrates that 19 amino acids supporting the binding of rutin inside the 1M48 protein. Specifically, Glu A:68, Thr A:41 and Arg A:38 amino acids formed hydrogen bonds with -OH (hydroxyl) group of the rutin molecule.

Figure 4: Secondary structure of protein 7JRA with binding pocket



Rutin binding pocket with active site amino acids. c. Salicylic acid interaction inside the binding pocket.

A total of 21hydrophopic amino acids play a major role, five hydrogen bonds by GlnC:137, Ser C:136, Ala A:232, Leu A:233, and Gly B:198 and 2 π- π ionic interaction aid the binding of rutin. But the salicylic acid only formed 2 interactions which made it less stable inside the binding pocket.

Figure 5: Rutin interaction with 1M48	Figure 6: Rutin interaction with 7JRA
	

Glide docking revealed that Rutin molecule accommodated inside the binding pocket of both IL-2 (1M48) as well as TNF-α (7JRA) proteins.

- The binding affinity of the molecule was found to be -5.485 kcal/mol and MMGBSA bind value of -41.58 kcal/mol with the IL-2 protein.
- Similarly, rutin's binding energy with TNF-α (7JRA) protein had been -10.841 & -71.58 kcal/mol.
- Amino acids supporting binding of rutin inside the 1M48 protein.
- Glu A:68, Thr A:41 and Arg A:38 amino acids formed hydrogen bonds with -OH (hydroxyl) group of the rutin molecule.
- Phe A:42 formed two π-π bonds with the interacting with chromon ring of the rutin.
- Hydrophobic amino acids such as Leu B:105, Ala B:109, Ala B:111, Ala A:73 and Leu A:72 aids the rutin molecule to properly orient inside the binding cavity.
- The reports of glide docking studies revealed that the, Rutin moiety formed proper pose inside the binding pocket of both the IL-2 (1M48) and TNF-α (7JRA) protein.

- The binding affinity of the molecule was found to be -5.485 kcal/mol and MMGBSA bind value of -41.58 kcal/mol with the IL-2 protein.
- Similarly, rutin's binding energy with TNF-α (7JRA) protein measured -10.841 & -71.58 kcal/mol.
- Amino acids supporting binding of rutin inside the 1M48 protein.
- Glu A:68, Thr A:41 and Arg A:38 amino acids formed hydrogen bonds with -OH (hydroxyl) group of the rutin molecule.
- Phe A:42 formed two π-π bonds with the interacting with chromon ring of the rutin.
- Hydrophobic amino acids such as Leu B:105, Ala B:109, Ala B:111, Ala A:73 and Leu A:72 aids the rutin molecule to properly orient inside the binding cavity.

Formulation of *Rivea hypocrateriformis* gel

- Z1 to Z7 Gel formulation was performed with Ethanolic leaf extracts of *R.hypocrateriformis*
- The percentage of cumulative drug release was better for the Z4 gel formulation
- The obtained data indicate the drug release, follows the principle of First, Higuchi, Peppas, and Hixson Crowell due to comparatively higher R-value.
- By means of Rheological parameter suitable formulation was chosen.
- Among all the parameter Z4 formulation proceed for further studies.
- A novel approach in formulating gel is the first attempt in this research
- Due to the presence of large concentration of flavonoid and other components in this formulation the research is continued for its pharmacological screening.

Table 3: Formulation of Gel

Code No	Extract (mg)	Carbopol 934 (gm)	Propylene glycol (gm)	Methyl Paraben (gm)	Glycerine (ml)	Tri ethanol amine (ml)	Water (ml)
Z1	0.5	8	150	Qs	0.5	Qs	33%
Z2	0.5	7.9	155	Qs	1	Qs	33%
Z3	0.5	7.7	160	Qs	2	Qs	33%
Z4	0.5	7.5	165	Qs	4	Qs	33%
Z5	0.5	7.3	170	Qs	6	Qs	33%
Z6	0.5	7.1	175	Qs	8	Qs	33%
Z7	0.5	7.0	180	Qs	10	Qs	33%

Table 4: Drug Release

Time (hr)	Percentage of cumulative drug release(hr)						
	Z1	Z2	Z3	Z4	Z5	Z6	Z7
0	0	0	0	0	0	0	0
1	4.36	9.86	8.82	9.20	5.65	5.31	7.33
2	12.33	22.76	16.22	22.34	14.33	25.6	18.25
4	18.36	27.49	23.42	35.27	18.89	34.89	20.31
6	21.63	30.47	27.75	44.65	20.96	45.15	25.03
8	23.33	35.56	32.04	51.84	29.35	54.47	31.05
10	50.32	68.42	61.71	76.76	50.36	74.66	65.56
12	75	77.68	75.3	85.89	76.55	86.81	72.36
24	85.25	91.82	87.15	**99.37**	88.37	99.25	79.02

Table 5: Drug Release Kinetics

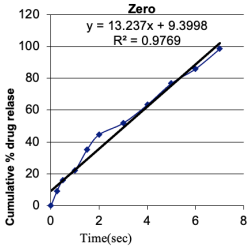
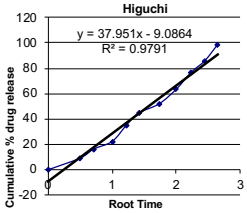
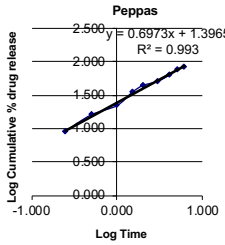
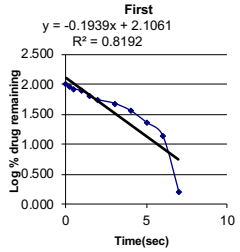
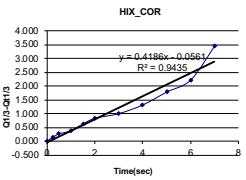
	Release Kinetics				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**	**Hixson Crowell**
	1	**2**	**3**	**4**	**5**
	R(CvT)	**R(CvRoot(T))**	**Log T vs Log C**	**TIME vs LOG % REMAINING**	**TIME Vs. (Q1/3-Qt1/3)**
Slope	13.237	37.951	0.700	-0.014	0.419
Correlation	0.9884	0.9895	0.9945	-0.9051	0.9713
R 2	0.9769	0.9791	0.9890	0.8192	0.9435
Figure 7: Cumulative percentage Drug release					

Table 6: Physical Parameters

Code	Spreadability (cm/sec.)
Z1	13.67
Z2	14.65
Z3	13.97
Z4	12.41
Z5	14.57
Z6	15.02
Z7	14.38

Table 7: Viscosity of the Sample

RPM (Revolution per Minute)	Z1	Z2	Z3	Z4	Z5	Z6	Z7
1	1746	390	431	1848	864	762	1260
1.5	1704	370	429	1720	858	720	1204
2	1656	357	427	1632	857	681	1137
2.5	1603	338	426	1577	854	660	1080
3	1566	325	424	1522	847	640	1050
4	1438	311	431	1462	836	635	1000

Table 8: Physical data of the sample

RPM (Revolution per Minute)	Visual appearance	Clarity	pH
Z1	Transparent	Clear	6.3
Z2	Transparent	Clear	6.2
Z3	Transparent	Clear	6.4
Z4	Transparent	Clear	6.2
Z5	Transparent	Clear	6.5
Z6	Transparent	Clear	6.4
Z7	Transparent	Clear	6.2

The diffusion mechanism of drug release was confirmed by Higuchi and Peppas.

- Drug release kinetics follows the principles of First order, zero order, Higuchi, Peppas, and Hixson Crowell and gives comparatively higher R-value.
- The drug release followed an anomalous transport which means the diffusion is time dependent.
- Brookfield viscometer LVDV-E model is used for measuring the viscosity parameter
- For the Anti-Inflammatory & Anti Psoriatic activity, Z4 *R.hypocrateriformis* gel formulation is chosen in Studies.

IN- VIVO STUDY

Imiquimod-induced psoriasis in rat model

Psoriasis has been caused by employing 5 percent Imiquimod cream on Wistar rats. The control and drug-induced groups had been observed for 14 days, after which the animals had been sacrificed and then subjected to histopathological analysis.

- To induce psoriasis in rats imiquimod-induced psoriasis mouse model had been employed.
- Administration of the IMQ medication to the mice for seven consecutive days resulted in an appearance of erythema, scaling, & skin thickening.
- Acute skin irritation test of plant gel does not show any skin incompatibility even at high concentrations.

Table 9: Acute skin irritation test for gel of *Rivea hypocrateriformis*

Group	Treatment	Gender	Number of animals (Wistar Rats)
1	Test sample High dose 400mg/kg	Male and Female	3
2	Test sample Mid dose 200mg/kg	Male and Female	3
3	Test sample Low dose 100mg/kg	Male and Female	3
Duration	14 Days	Total	9

Table 10: PASI grading of psoriasis animals after Induction (Imiquimod 5%)

SCORE	0	1	2(5th Day)	3(6th Day)	4(7th Day)
Erythema (redness)	Fleshy pink	Minor redness	Medium red	Medium reddish scars	Dark reddish skin
Induration (thickness)	Absence of thick skin	Visible skin thickness	Skin thickness (1-2mm)	Skin thickness>2mm	Skin thickness>2mm
De-squamation (scaling)	Absence of thick skin	Minor dry spots	Moderate flakes on skin	Moderate flaking	Mild flakes around the skin

Table 11: PASI grading of psoriasis animals after treatment

Score	3(8th Day)	2(10th Day)	1(12th Day)
Erythema (redness)	Medium red	Minor reddening	No red spots
Induration (thickness)	Skin thickening	Minor skin thickness	Slight changes
De-squamation (scaling)	Skin thickening	Moderate red spots	Minor flaking

Figure 8: Effect of Plant Gel extract on Psoriasis score

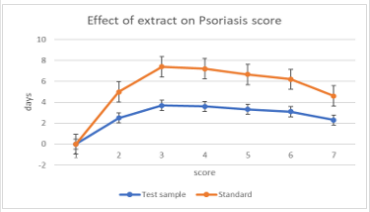


Figure 9 Before Induction

Figure 10 After Induction of Imiquimod cream 5%w/w

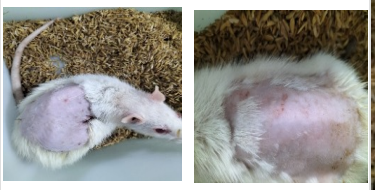
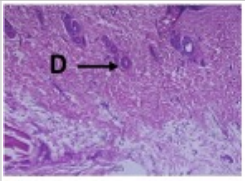
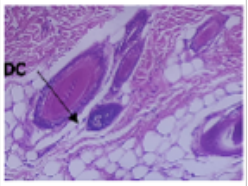
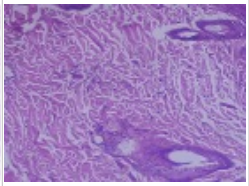
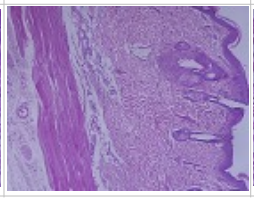
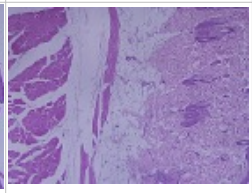
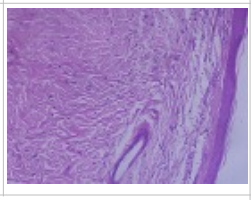


Figure 11 After treatment with plant extract Gel

Figure 12: Control, Salicylic acid, *R.hypocrateriformis* gel extracts

Control (Dermal Layer)	Imiquimod 5%w/w (Degenerative changes)	Standard 1% Salicylic acid (Regenerative changes)	Herbal gel extracts 100mg/kg (Orthokerotosis)	(Regenerative changes)	
				Herbal gel extracts 200mg/kg	Herbal gel extracts 400mg/kg
					

DC-Dermal layer, HF-Hair follicle, OR-Orthokerotosis, RC-Regenerative changes, DC-Degenerative changes, E-Epidermal layer

The scoring severity of skin inflammation was studied by the PASI score method**.** Hematoxylin and Eosin staining technique are used for histopathological studies with 10x fold magnification.

Histopathological analysis

Histopathological analysis of the skin and Pasi (Psoriatic Area and Severity Index) ratings (zero, mild, moderate, and severe) were used to determine the efficacy of Rh herbal gel in the treatment of psoriasis in Fig 12.

- **Histological analysis** of imiquimod-treated skin samples reveals severe tissue damage as evidenced by a degenerative change in the epidermis, increased keratinization, a **decrease in the percentage of orthokeratosis regions**, the elongation of rete ridges, the dilation of capillary loops, and the presence of minimal grade lesion of Munro's micro abscess.
- The normal cytoarchitecture of skin tissue in animals treated with Salicylic acid and herbal gel extracts is indicative of **regenerative processes.**
- Treatment with *R. hypocrateriformis* resulted in a significant recovery from atopic psoriasis in the treated groups, evidenced by a notable reduction in skin thickness & scaling, along with a decreased PASI scale grading in these groups.

Histopathological results indicate that topical therapy with *R. hypocrafteriformis* resulted in enhanced tissue integrity, characterized by increased collagen content, angiogenesis, and keratinization, with fibroblast proliferation concerning the control group.

- On accounting for increased concentration of Flavonoids such as Rutin explore its activity with the binding proteins such as IL2 and TNF-α results in inhibitory mediators compared with standard Salicylic acid.
- *R. hypocrateriformis* gel of 400mg/kg slowly exhibits the regeneration of cells compared to 1% salicylic acid.
- *R. hypocrateriformis* can be comprised of other convolvulaceae species and anticipate better potential health for the psoriatic conditions.
- Regeneration of cells slowly develops resulting in a reduction of scaling and erythema.

- On account of the moisturizing and healing effect of the plant, the gel would help to restore skin elasticity.
- This *in vivo* study was conducted to ensure the safety of prolonged treatment of herbal topical gel and should be biocompatibility in specific skin-sensitive areas.
- Frequent application of this topical gel slowly treats the Atopic type of psoriasis and flares in the skin.

Discussion

Rivea hypocrateriformis is a climbing shrub it has been found in subtropical forest under Convolvulaceae species with enormous medicinal benefits. Most of the Convolvulaceae species are called as morning glory because they bloom early and wilt by afternoon. Many research works had been carried out in this species, that includes Pharmacognostical studies, Pharmacological, Phytochemical, Isolation and Estimation of phenolic and flavonoid content. Previously study conducted reports the microscopical features of *R.hypocrateriformis* leaves consist of Palisade cells, thin layered epidermis, vascular bundle, spongy parenchyma, collenchymatous cells, xylem vessels aleurone grains, paracytic stomata, and starch grains.

In this research the *R.hypocrateriformis* leaves was collected at different districts and it proves to have similar microscopical and macroscopical characters does not reveals any new cellular structures. Earlier Phytochemical investigation performed in aerial parts and roots of *R.hypocrateriformis* shows the presence of Alkaloids, glycosides, Phenol, Flavonoids and Tannin content, the study presided in leaves of this species exhibited the presence of flavonoids, carbohydrates, proteins, terpenoids, tannin, and coumarin glycosides.Apart from *R.hypocrateriformis* some of the selected taxa of Convolvulaceae showed possess more phytoconstituents compared to stem, the important phytochemicals are flavonoids, carbohydrates, alkaloids, glycosides, proteins, phytosterols, and phenolic compounds, whereas there is a lesser concentration of phytoconstituents in stem that includes carbohydrates, saponins and phenolic components. Mostly flavonoid are utilized to prevent cell damage. Tannins present are used as astringent, antiseptic, anti-inflammatory and anti-oxidants.

Some of the alkaloids in Convolvulaceae species are used for curing psychological conditions many Indole and Ergoline alkaloids are also responsible for this, which was found in Convolvulaceae species like *Ipomoea violaceae* (L.) and *Turbina corymbose* (L.) also acting as a narcotic drug.

Saponins and phenolic compounds are present which promote nutraceuticals and protect plants from the attack of microorganisms. Besides this, the presence of polyphenolic compounds prevents the growth of tumors, diabetes, and cardiovascular and neurodegenerative diseases. Phytosterols present functions in detecting malignancies like prostate cancer. Glycosides show a beneficial effect on the human immune system, and because of these wide ranges of phytoconstituents Convolvulaceae species had been selected in this research.

Polyherbal combination of Convolvulaceae species has been used in managing insomnia and neurodegenerative diseases. *Ipomea alba. Ipomea pileate, Ipomea purpurea* the leaves and latex obtained from the above species is used to treat skin diseases that come under the Convolvulaceae family. *Argyreia* species are also used for treating boils, warts removal, and leprosy infections. In this research treating psoriasis like eczema and dermatitis type of symptoms it was the first study conducted in *R.hypocrateriformis* with the availability of the above ethnomedicinal information.

A few genera like *Cuscata reflexa, Cuscata pedicellate, and Cuscata racemose* are Convolvulaceae species that have been evaluated for antibacterial, antifungal, and antiviral studies, it was tested for gram-negative, gram-positive fungal and yeast infections *Evovulus alsinoides* a Convolvulaceae species whose roots portion is dried, powdered and used in case of poisonous snake bites. The above information indicates that Convolvulaceae species can also be involved in treating poisonous venom and snake bites. Conservation of these species is important to prevent their vanishing due to the changes in habitat

Earlier isolation was carried out in the stem portion of *R.hypocrateriformis* proved to have a secondary metabolite flavonoid as Bergenin and Rivebergenin A&B. Previous studies proved to have an Inhibitory action in swelling and arthritis due to its increased concentration of phenolic content. *R.hypocrateriformis* plant also shows interruption of pregnancy in female albino rats and is also used in ayurvedic formulation as a psychoactive agent. This research was about to correlate all the studies by investigating its phytoconstituents and further proceed for the formulation then cell lines studies and also psoriatic activity

Research undergone in this species was reported for anti-ontogenetic, hepatoprotective, anti-infertility, and analgesic, Trton induces hyperlipidemia and reduces the lipid peroxidation enzyme. The above pharmacological studies were performed in the roots and aerial parts of *R.hypocrateriformis*. By gathering this scientific evidence a research was persuaded by formulating the leaf extracts of *R.hypocrateriformis* into gel. Evaluation of the gel was done with the following parameters pH, spreadability, viscosity, and transparency. The cumulative percentage of drug diffusion indicate by extending the release of the drug.

Most of the kinetic models involved are first order, zero, Higuchi, Peppas, Hixson Crowell which determine the release profile of gel. The regression coefficient value (R^2=0.9890) was found suitable for the gel of *R.hypocrateriformis* which is permeable through the rat skin. Release exponent value is expressed as 0.8192 which shows that the release mechanism is non-Fickian. Thus the gel was significantly penetrated through the rat skin the stability study proves that there is no significant difference in spreadability, viscosity, and appearance so it remains stable. Most often psoriasis is related to inflammation and arthritis it was related in this research work by performing a cell line study with RAW 264.7 murine macrophage cell line which reveals a remarkable effect in inhibiting Nitric oxide production.

Many marketed herbal formulations were available for curing psoriasis to minimize the side effects of steroids and synthetic drugs. Topical gel formulation has a great advantage on behalf of this gastrointestinal drug absorption difficulties can minimised. Ethnomedicinal information about this plant provides knowledge of Convolvulaceae species that can be used for curing skin ailments, based on this novel research was conducted with Imiquimod-induced psoriasis in rats, with different concentration of *R.hypocrateriformis* gel compared with standard salicylic acid. The formulated gel gives better anti-inflammatory and psoriatic activity with good consistency and stability.

After induction of imiquimod in the rat skin it caused reddish scale patches which were slowly cured by *R.hypocrateriformis* gel, this was examined by histopathological changes such as degeneration, keratinocytes, and orthokeratosis. After applying the

gel of *R.hypocrateriformis* at different concentrations it regained regeneration of cells and the development of hair follicles was also observed when compared with standard 1% salicylic acid. Finally, it was justified with the above shreds of evidence that most of the Convolvulaceae species including *R.hypocrateriformis* as more therapeutic benefits and are effective in treating different diseases and ailments.

Conclusion

Natural products play a vital role in recent trends to cure various disease ailments. There should be an awareness of natural products through regular training programs in various healthcare settings to make effective services in treating diseases. Phytoconstituents extracted from diverse plants were studied for their potential impact on immune response throughout the psoriasis disease process. Thus, the usefulness of plant-derived medications in managing the inflammatory load on psoriatic patients by reducing oxidative stress circumstances is highlighted by the naturally derived plant products in controlling the system and maintaining long-term illnesses inactive without any side effects. Mild cases of Psoriasis first start with a dermatitis symptom, if left untreated leads to eczema and finally Psoriatic conditions. At an early stage the symptoms are managed by using certain herbal drugs, it also creates awareness among the public in the usage of plant species. Continuous patient education and counseling create an impact to cure such skin infections in the initial stage by proper diagnosis methods.

Nowadays skin diseases are common in both genders and they affect their day-to-day life, it can be stopped by changing the quality of Life. A questionnaire of the Psoriasis disability index was maintained among the patients to assess overall Psoriasis disability. By conducting the awareness program, it helps an affected individual to understand the entire mechanism and increase his confidence level to survive in society. Psychological stress is also one of the factors in triggering Psoriasis. A holistic care of an individual with Psoriasis is accomplished by Recognition and management of disease. In the case of affected individual self-esteem to be improved like surviving with Psoriasis is not a big task as it is a chronic disease it may take some time to cure entirely. Proper mitigation in early stage is the only way to prevent and manage the symptoms of Psoriasis. Execution of Aromatic and some essential oils also plays a vital part in subsidizing the Psoriatic condition.

Acknowledgements: Not applicable

Further Research is warranted to: Conventional therapy paves the way for treating skin diseases, and in future, other Convolvulaceae species prove to have a remarkable effect in treating atopic to Psoriatic type of skin diseases.

Conflict of Interest: No conflict of interest

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