ANTI – PSORIATIC EFFECT OF *Zingiber officinale roscae* GEL ON UV-RADIATION AND 5%w/w IMIQUIMOD CREAM INDUCED PSORIASIS IN WISTAR RATS

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI-600 032

In partial fulfilment of the requirements for the award of the degree of

MASTER OF PHARMACY
IN
BRANCH – IV– PHARMACOLOGY

Submitted by

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C.L. BAID METHA COLLEGE OF PHARMACY

OWNED AND MANAGED BY TAMILNADU CHEMISTS AND DRUGGISTS EDUCATIONAL TRUST

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CERTIFICATE

This is to certify that the Project entitled **"ANTI-PSORIATIC EFFECT OF *Zingiber officinale roscae* GEL ON UV-RADAIATION AND 5%w/w IMIQUIMOD CREAM INDUCED PSORIASIS IN WISTAR RATS"** was submitted by **MAHALAKSHMI.R (Reg. No: 261925005)** in partial fulfilment for the award of the degree of **Master of Pharmacy(Pharmacology)** by THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI- 600032**.** It was carried out at the Department Of Pharmacology in C.L. Baid Metha College of Pharmacy, Chennai-600097 under my Guidance and Supervision during the academic year 2020-2021.

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DECLARATION

Register No: **261925005** hereby declare that this dissertation entitled, **ANTI-PSORIATIC EFFECT OF *Zingiber officinale roscae* GEL on UV-RADAIATION AND 5% IMIQUIMOD CREAM INDUCED PSORIASIS IN WISTAR RAT** has been originally carried out by me under the guidance and supervision of **Prof. Dr. P.Amudha, M.Pharm,. PhD,** Department of Pharmacology C.L.Baid Metha College of Pharmacy, Chennai-97 for the academic year 2020-2021.This work has not been submitted in any other degree at any other university.

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LIST OF CHEMICALS

S.NO	CHEMICALS	SOURCE
1.	Acetic acid	S.d.fine chemicals Ltd, Mumbai
2.	Aluminium chloride	S.d.fine chemicals Ltd, Mumbai
3.	1% Ammonium hydroxide	S.d.fine chemicals Ltd, Mumbai
4.	10% Aqueous Hydrochloric acid	Loba chemicals Ltd, Mumbai
5.	Chloroform	S.d.fine chemicals Ltd, Mumbai
6.	Conc.Sulphuric acid	Loba chemicals Ltd, Mumbai
7.	Clobetasol Propionate cream 0.02%w/w	Glaxosmithkline Pharmaceuticals Maharashtra
8.	Ethanol	S.d.fine chemicals Ltd, Mumbai
9.	Ferric chloride	S.d.fine chemicals Ltd, Mumbai
10.	Felhing solution A	Loba chemicals Ltd, Mumbai
11.	Felhing solution B	Loba chemicals Ltd, Mumbai
12.	Formalin	Loba chemicals Ltd, Mumbai
13.	Glycerin	Sigma Aldrich Mumbai
14.	Hydrochloric acid	S.d.fine chemicals Ltd, Mumbai
15.	Hydroxy propyl methyl cellulose	Sigma Aldrich Mumbai
16.	Imiquimod cream 5% w/w	Glenmark Pharmaceuticals Mumbai
17.	Propylene glycol	Sigma Aldrich Mumbai
18.	Sodium chloride	Sigma Aldrich Mumbai
19.	Sodium Hydroxide	Loba chemicals Ltd, Mumbai
20.	Tretinoin gel 0.04% w/w	Sigma chemical Co., USA
21.	Triethanolamine	Loba chemicals Ltd, Mumbai
22	Tris buffer	Loba chemicals Ltd, Mumbai

LIST OF ABBREVATIONS

ACE inhibitors	Angiotensin converting enzyme inhibitors
ADP	Adenosine diphosphate
AMP	Anti-microbial peptides
AP- 1	Activator protein
APC	Antigen presenting cells
Camp	Cyclic adenosine monophosphate
CARD – 14	Caspase recruitment domain 14
CD	Cluster of differentiation
CHF	Chronic Heart Failure
Cm	Centimeter
CNS	Central Nervous system
DEN	Diethylenetriamine
DNA	Deoxyribonucleic acid
EtOH/HCL	Ethanol/Hydrochloric
FDA	Food and drug administration
FSN	Flaky skin
HPA	Hypothalamus pituitary adrenal
HPMC	Hydroxy propyl methyl cellulose
IBS-D	Irritable Bowel syndrome diarrhea
Ig	Immunoglobin
IL	Interleukin
Imq	Imiquimod
JAK	Janus kinase
K14/IL-36	Keratinocycte Interleukin – 36
Kg	Kilogram
LFA – 3	Leukocyte function associated antigen

Mm	Millimeter
NCD	Non-communicable disease
NF κ β	Nuclear factor kappa light chain
NHK	Normal human keratinocytes
Nm	Nanometer
NSAIDS	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PASI	Psoriasis area and severity index
PDE- 4	Phosphodiesterase – 4
PMN	Polymorphonuclear leukocyctes
PSA	Psoriasis
PSA	Passive avoidance learning
QOL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomized controlled trials
STZ	Streptozotocin
SEM	Standard error mean
TGF – β	Transforming growth factor
TH	T – helper cells
TLR	Toll-like receptor
UC	Ulcerative colitis
UV	Ultraviolet
ZOR	Zingiber officinale rosace

INTRODUCTION

1. INTRODUCTION

PSORIASIS:

Psoriasis is a chronic, non-communicable, painful, disfiguring and disabling disease for which there is no cure and with great negative impact on patients' quality of life (QoL). It can occur at any age, and is most common in the age group 50–69. The reported prevalence of Psoriasis in countries ranges between 0.09% and 11.4%, making Psoriasis a serious global problem. The Etiology of Psoriasis remains unclear, although there is evidence for genetic predisposition. The role of the immune system in Psoriasis causation is also a major topic of research.

Although there is a suggestion that Psoriasis could be an autoimmune disease, no auto antigen that could be responsible has been defined yet. Psoriasis can also be provoked by external and internal triggers, including mild trauma, sunburn, infections, systemic drugs and stress. Psoriasis involves the skin and nails, and is associated with a number of comorbidities. Skin lesions are localized or generalized, mostly symmetrical, sharply demarcated, red papules and plaques, andusually covered with white or silver scales. Lesions cause itching, stinging and pain. Between 1.3% and 34.7% of individuals with Psoriasis develop chronic, inflammatory arthritis (Psoriatic arthritis) that leads to joint deformations and disability. Between 4.2% and 69% of all patients suffering from Psoriasis develop nail changes. Individuals with Psoriasis are reported to be at increased risk of developing other serious clinical conditions such as cardiovascular and other non- communicable diseases (NCDs). Psoriasis causes great physical, emotional and social burden. Disfiguration, disability and marked loss of productivity are common challenges for people with Psoriasis. There is also a significant cost to mental well-being, such as higher ratesof depression, leading to negative impact for individuals and society.

Social exclusion, discrimination and stigma are psychologically devastating for Individuals suffering from Psoriasis and their families. It is not Psoriasis causing the exclusion – it is largely society's reaction to it and this can change. Treatmentof Psoriasis is still based on controlling the symptoms.

Topical and systemic therapies as well as phototherapy are available. In practice, a combination of these methods is often used. The need for treatment is usually life long and is aimed at remission. So far, there is no therapy that would give hope for a complete cure of Psoriasis. Additionally, care for patients with Psoriasis requires not only treating skin lesions and joint involvement, but it is also very important to identify and manage common comorbidity that already exists or may develop, including cardiovascular and metabolic

diseases as well as psychological conditions. [1]

Fig no: 1 Psoriasis

1.1 TYPES OF PSORIASIS:

Plague Psoriasis:

Chronic plaque Psoriasis (Psoriasis vulgaris) is the most common form of the disease, and accounts for about 90% of cases. Typical lesions are monomorphic, sharply demarcated erythematous plaques covered by silvery lamellar scales.

Plaques can be few they can extend over larger areas and they can also present aserythroderma affecting the entire body surface. [2]

Guttate Psoriasis:

Guttate Psoriasis is an acute eruption of small plaques, typically up to 1 cm in diameter, distributed over the trunk and often involving the limbs following upper respiratory tract infection. Streptococcal sore throats are the most important trigger. The differential diagnosis includes pityriasis versicolor and pityriasis rosea.Management includes topical treatments, UVB and tonsillectomy, which may be helpful when the condition is associated with recurrent tonsillitis.

Palmoplantar Pustular Psoriasis:

It is a common Pustular eruption involving the palms and soles, seen predominantly in female patients. The disease tends to have a chronic relapsing course. Pustules develop in crops, changing from white to brown before gradually fading the inflammation causes severe erythema, scaling and soreness. The relationship between this condition and other variants of Psoriasis is controversial because it is often seen in isolation, without Psoriatic lesions elsewhere. Palmoplantar Pustular Psoriasis does not often evolve into generalized forms of Pustular Psoriasis.

Generalized Pustular psoriasis:

This life-threatening variant of Psoriasis often erupts suddenly in individuals with no past history of the disease. Some cases appear to be triggered by withdrawal of systemic or topical corticosteroids. Sheets of small pustules often merge to form 'lakes' of pus and spread in waves across the body and limbs on an erythematous and often Edematous base. The flexures are often prominent sites of pustulation. Patients are often pyrexia and systemically ill. Complications include hypo-albuminemia, dehydration, hypocalcemia, septicemia and hypothermia.

Erythroderma Psoriasis:

The history is therefore important because the clinical findings may be identical to those seen in exfoliative Psoriasis arising from other diseases. Erythrodermic patients are at grave risk of septicemia, hypothermia and dehydration. Elderly patients are particularly vulnerable and may deteriorate rapidly. [3]

Nail changes

Nail changes include pitting, onycholysis and subungual hyperkeratosis these reflect Psoriatic changes in the nail matrix and nail bed. A pink or yellowish area often occurs beneath the nail, adjacent to the free margin or an area of onycholysis ('oil-drop sign'). Less often, subungual splinter hemorrhages are seen. The differential diagnosis includes Psoriasis and alopecia areata, which cause pitting, whilst drug reactions or phototoxic reaction (e.g. during PUVA therapy) may cause onycholysis. Subungual hyperkeratosis is a feature of dermatophyte infection, which may coexist with Psoriatic nail dystrophy. Onycholysis. Subungual hyperkeratosis is a feature of dermatophyte infection, which may coexist with Psoriatic nail dystrophy. [4]

Flexural and genital Psoriasis:

The appearance of flexural Psoriasis differs fromlesions elsewhere in that, although it is erythematous, it is not usually scaly Exudation may be prominent. The clear margination of the lesions is a useful diagnostic feature. [(9)(4)]

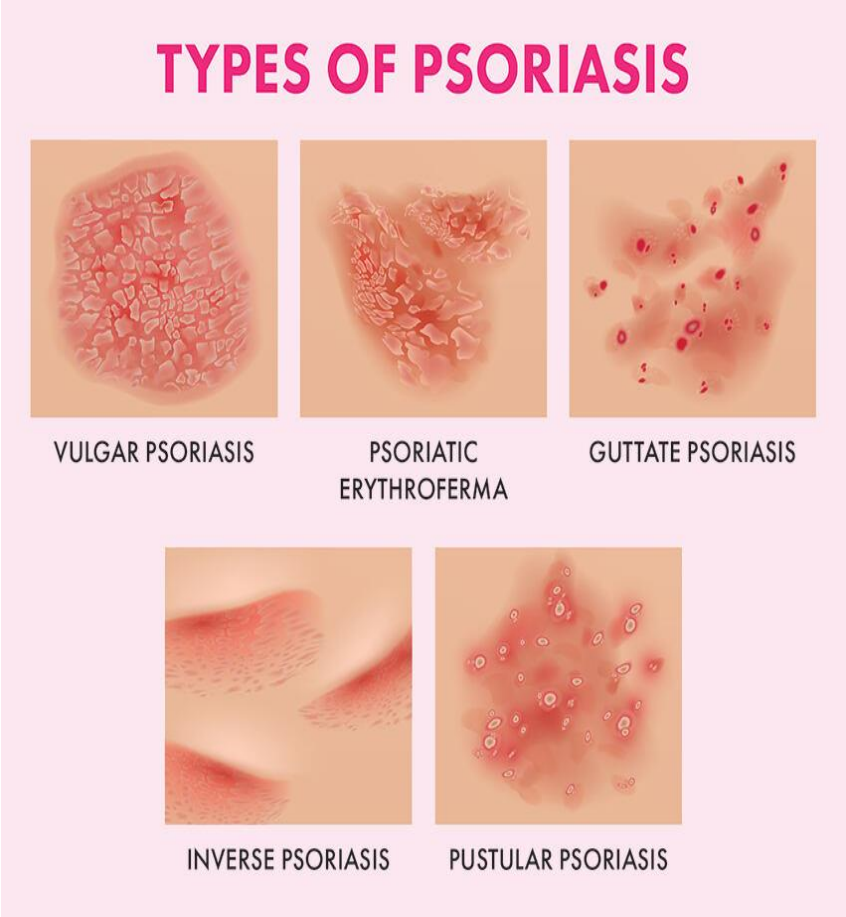


Fig no: 2 Typesof psoriasis

1.2 PATHOGENESIS OF PSORIASIS:

The pathophysiology of Psoriasis is not completely understood. It involves multiple factors, including genetic, immunologic, environmental, stress factors contributing to the development ofdisease.

Activated T cells are believed to be the primary modulators in the pathogenesis of Psoriasis. Disordered cellular immunity involving inflammatory cytokines (IL-1 (interleukin-1)

IL-6(interleukin-6) Tumor necrosis factor-α [TNF-α]) and proinflammatory transcription factor NF-κB (nuclear factor kappa light chain) signal transduction and transcription and AP-1 Activator protein) has also been implicated. Naïve T-cells can differentiate into any of the four types of inflammatory cells. Th1 (T helper1) Th2, Th17 or T regulatory cells) depending on the presence of TNF-α, (tumor necrosis factor) TNF-β and IL-6(interleukin). In the presence of TGF-β (transforming growth factor) and IL-6, naive T-cells transform into Th17 cells. These activated cells enter the circulation and extravasate through the endothelium to the sites of inflammation in skin where they produce the Th1-Th2-Th17 imbalance. The role of the IL-23/Th17(Interleukin-23/T helper17) pathway has been intensely researched in recent years. IL-23, a heterodimer composed of p19 and p40 subunits, is produced by dendritic cells and macrophages. It causes activation of Th17 cells to produce IL-17 (Interleukin-17) and IL-22(Interleukin-22). Psoriatic skin lesions contain high mRNA IL-23 levels compared to normal skin. Th17 cells are CD4+ (cluster of differentiation) effector cells distinct from the classic Th1 and Th2 lineages and Responsible for providing both innate and adaptive immunity against pathogens. IL-17 (also known as IL-17A) is part of a group of cytokines, called the IL-17 family, consisting of six ligands (A to F), and with five receptor family members. IL-17 cytokines are probably critical for the pathogenesis of Psoriasis. IL-17A and IL- 17F are the predominant cytokines released by Th17 cells, but are also produced by T cells, whereas IL-17C is produced by keratinocytes.

IL-17A and IL-17F act on keratinocytes to stimulate the production of β-defences and antimicrobial Peptides (AMPs) adenosine mono phosphate and chemokine's such as IL-8. In addition, the IL-17 system may also play a role in antimicrobial defence via maintenance of mucocutaneous immunity. Elevated levels of IL-17 result in an increase in levels of pro-inflammatory cytokines like S-210, A7, β-defensins and lipocalin. In addition, increased levels of β-defensins are associated with relative resistance to infections. Increased levels of IL-17 also promote keratinocytes to produce CXC-chemokines and CCL-20(chemokine ligand 20), both of which attract neutrophils to the site of inflammation. Increased IL-22 levels lead to epidermal acanthosis and abnormal keratinocyte differentiation.

The role of a new subtype of cells, Th-22 cells, is also considered important in the pathogenesis of Psoriasis. These cells, on activation by TNF-α, IL-6 and CCL20, exclusively produce IL-22 and are involved in epidermal immunity and remodeling. [(5)]

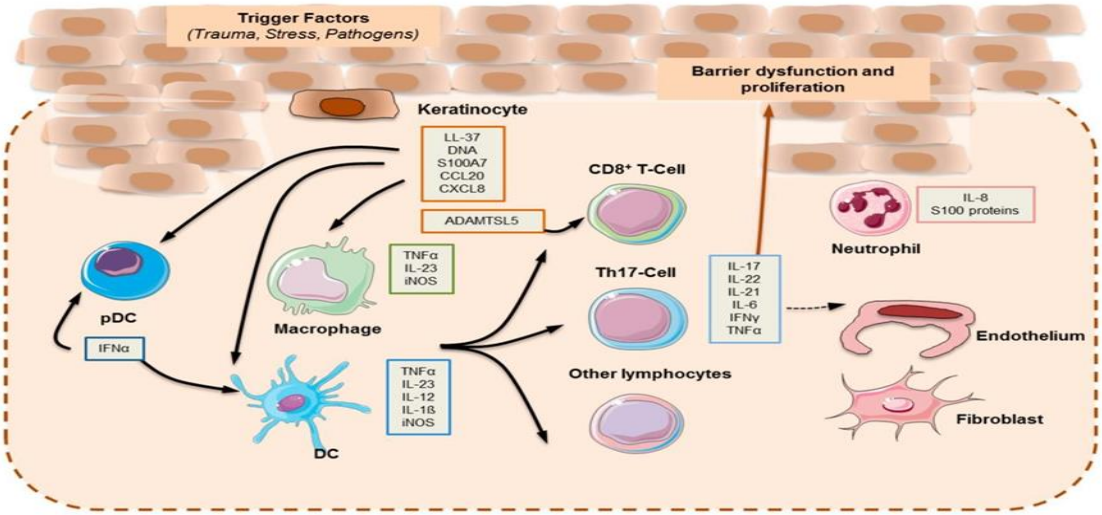


Fig no: 3 Pathogenesis of psoriasis [5]

1.3 PATHOPHYSIOLOGY OF DIFFERENT TYPES OF PSORIASIS:

Pustular psoriasis:

Pustular psoriasis is caused by 7 Genetic analyses have identified interleukin- 36RN mutations and a caspase recruitment domain family member CARD14 (Caspase Recruitment Domain) gain-of-function mutation as important predisposing factors of psoriasis variants. Most cases of generalized Pustular psoriasis alone are caused by recessive mutations of interleukin 36RN, but very few cases of generalized Pustular psoriasis with psoriasis vulgaris have recessive interleukin-36RN mutations, which suggests that generalized Pustular psoriasis alone is genetically different than when combined with psoriasis vulgaris. Identification of recessive interleukin-36RN mutations leads to early diagnosis of generalized Pustular psoriasis, and a CARD14 gain-of-function mutation is a predisposing factor for generalized Pustular psoriasiswith psoriasis vulgaris. [6]

Erythrodermic psoriasis:

The pathogenesis of Erythrodermic psoriasis include abnormal interactions between T-lymphocytes, dendritic cells, keratinocytes, neutrophils, and proinflammatory cytokines, leading to activation of the Th17 and Th1 immuneaxes. [7]

Nail psoriasis:

The nail lesions were believed to represent an abnormal response to tissue stressingof the integrated nail-joint apparatus, rather than being due to autoimmunity.

The nail and joint disease may be linked to tissue-specific factors, including tissue biomechanical stressing and micro trauma that led to activation of aberrant innate immune responses. However, a case of skin and nail psoriasis definitely disappearing after allogeneic

bone marrow transplantation is more in favor of predominant immunogenic factors. [8]

Psoriatic arthritis:

Researchers sought to define the role of Th17 cells in inflammatory arthritis. In RA and PsA, serum levels of IL-17 were not elevated compared with healthy controls. However, an increased percentage of IL-17-producing cells was identified in both RA (Rheumatoid arthritis) and PsA (Psoriatic arthritis) compared with controls when peripheral blood T cells are stimulated ex vivo. Moreover, the CD41 IL-17 1 subset was present at higher levels in RA and PsA synovial fluid, whereas CD81 IL-17 T cells were elevated only in PsA synovial fluid. Furthermore, the number of CD81 IL-17- producing cells in the PsA patients correlated with disease activity and musculoskeletal ultrasound signals. These findings suggest that CD41 IL-171 cells contribute to inflammation in rheumatoid and psoriatic joints, while the IL-17 response in psoriatic synovial tissues involves CD4 cells, specifically, CD81 cells and innate lymphocytes. [9]

1.4 ETIOLOGY:

Trauma: Psoriasis at the site of injury is well known and the Phenomenon is termed as Koebner phenomenon. A wide range of injurious local stimuli, including physical, chemical, electrical, surgical, infective and inflammatory insults have been recognized to elicit psoriatic lesion.

Environmental factors: several studies validated that the interaction between genes and environment is important in manifestation of psoriasis. Many environmental factors have linked to psoriasis, and have been implicated in the manifestation of disease and exacerbation of pre-existing disease.

Infection: Acute Guttate psoriasis is strongly associated with proceeding or concurrent streptococcal infection, particularly of the throat. There is evidence that streptococcal infection may be important in chronic plaque psoriasis, and treatment with rifampicin and penicillin may lead to clearance of skin lesions.

Drugs: There are many drugs reported to be responsible for the onset or exacerbation of psoriasis. Chief amongst these are lithium salts, antimalarial, beta blockers, ACE inhibitors, NSAIDS, and the withdrawal of corticosteroids. Some authors and colleagues have suggested that NSAIDS and beta blockers have little adverse effect but the adverse effect of lithium salts and antimalarial may be severe.

Metabolic factors: The early onset of psoriasis in the women, with a peak around puberty, changes during pregnancy and provocation of psoriasis by high dose estrogen therapy

potentially indicate a role for hormonal factors in the disease.

A questionnaire study has provided data from 65 females who had one or more pregnancies after diagnosis was made. Psoriasis was improved approximately in

40% of the pregnancies, and worsened in 14%. Hypocalcaemia has been reported to occur in severe forms of psoriasis, particularly generalized Pustular psoriasis.

Psychogenic factors: Considerable clinical evidence exists for the role of psychogenic factors in onset and exacerbation of disease. Seville reported consistent links between major stressful life events and disease manifestation. Gupta reported more exacerbations and worsening of disease related with stress reactivity Some other studies also established the role of psychogenic factors in the initiation or exacerbation of psoriasis

Alcohol and smoking: It have long been suspected that both cigarettes and alcohol have a detrimental effect on psoriasis. When controlled for confounding variables, studies suggested that alcohol may exacerbate preexisting disease but does not appear to induce psoriasis.

This effect seems greater in men than women. Heavy drinkers tend to have more extensive and inflamed disease. Increased alcohol consumption is a recognized stress response. Excess drinking is undoubtedly also a consequence of disease and leads to treatment resistance and reduces therapeutic compliance.

Weather: Winter tends to be the most challenging season for people living with psoriasis. Numerous studies indicate cold weather is a common trigger for many people and that hot and sunny climates appear to clear the skin. Cold winter weather is dry, and indoor heat robs the skin of needed moisture. This usually worsens psoriasis. Psoriasis can become even more severe when the stress of the holidays and winter illnesses combine to compromise immune system. While hot and sunny may help clear psoriasis, air conditioning can dry out the skin and aggravate psoriasis.[10]

1.5 GLOBAL BURDEN:

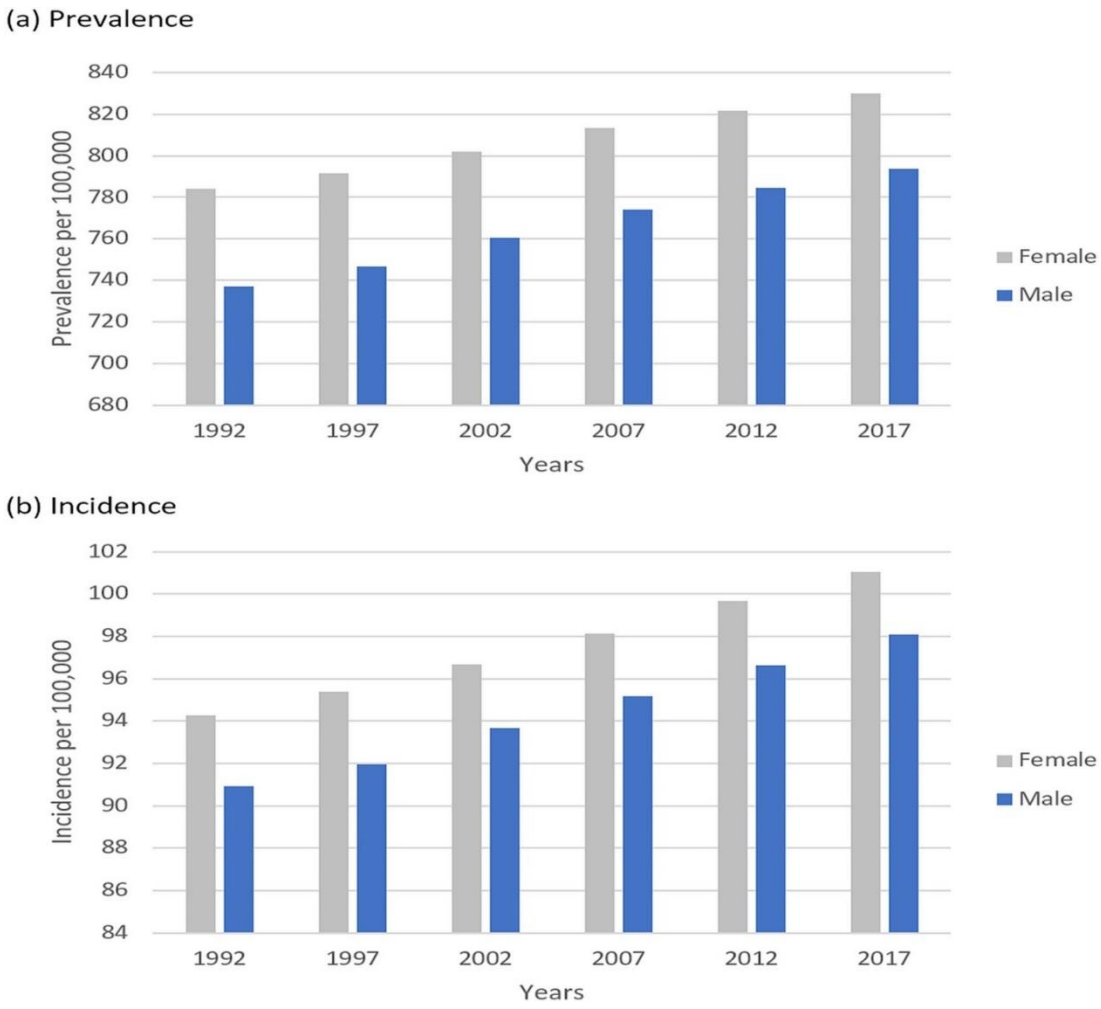


Fig no: 4 Global Burden of Psoriasis

1.6 CLINICAL FEATURE:

Psoriasis is a Papulosquamous disease with variable morphology, distribution, severity, and course. Papulosquamous diseases are Characterized by scaling papules (raised lesions,1 cm in diameter) and plaques (raised lesions .1 cm in diameter). Other Papulosquamous diseases that may be considered in the differential diagnosis include tinea infections, pityriasis rosea, and lichen planus. The lesions of psoriasis are distinct from these other entities and are classically very well circumscribed, circular, red papules or plaques with a grey or silvery-white, dry scale. In addition, the lesions are typically distributed symmetrically on the scalp, elbows, knees, lumbosacral area, and in the body folds. Psoriasis may also develop at the site of trauma or injury, known as Koebner's phenomenon. If psoriasis is progressive or uncontrolled, it can result in a generalized exfoliative erythroderma.

0Nail involvement may be present, particularly if psoriatic arthritis (PsA) is present. Occasionally psoriasis may involve the oral mucosa or the tongue. When the tongue is involved, the dorsal surface may have sharply circumscribed gyrate red patches with a white yellow border. The patches may evolve and spread, changing on a daily basis, can assume distinct annular patterns and may resemble a map, hence the term geographic tongue. Psoriasis can be highly variable in morphology, distribution, and severity. Despite the classic presentation described above, the morphology can range from small tear shaped papules (Guttate psoriasis) to pustules (Pustular psoriasis) and generalized erythema and scale (Erythrodermic psoriasis). In addition, these different forms of psoriasis may be localized or widespread and disabling. Further, psoriasis may have a variable course presenting as chronic, stable plaques or may present acutely, with a rapid progression and widespread involvement. Psoriasis may be symptomatic with patients complaining of intense pruritus or burning. [(12)]

1.7 DIAGNOSIS OF PSORIASIS:

Dermatological examination

Psoriasis lesions consist of red, inflamed patches of skin with erythematous macules, that progress into maculopapules and well-demarcated, noncoherent, raised plaques with white micaceous scale, overlying a glossy homogeneous erythema the dry flakes of skin scales result from the excessively rapid proliferation of skin cells triggered by inflammatory responses, the rapid overproduction leading to the buildup of skin cells. Lesions may vary in

size (from pinpoint papules to large plaques) and in distribution, but are usually found symmetrical on the scalp, post auricular skin, elbows, back, gluteal cleft, and knees. Clinical findings are variable among patients and can change quickly within the same patient even after plaques have cleared, permanent dyschromia may be present. For psoriasis lesions, the dermatologist should also check the nails, oral mucosa and tongue for specific signs of psoriasis

Skin biopsy:

Most cases of psoriasis are diagnosed clinically, but some Pustular forms are difficult to recognize. Punch biopsy of the skin may act as a confirmatory workup procedure for atypical cases and exclude other conditions in cases of diagnostic uncertainty atopic Psoriasis (eczema), tinea corporis (ringworm), pityriasis rosea or rubra pilaris, seborrhea Psoriasis, etc. Biopsy of acral skin may be less useful for the clinician as chronic eczematous Psoriasis may be psoriasiform, while psoriasis of the palms and soles may show spongiosis more often associated with eczema.

You may be referred to a specialist in diagnosing and treating skin conditions (dermatologist) if your doctor is uncertain about your diagnosis, or if your condition is severe. If doctor suspects you have psoriatic arthritis, which is sometimes a complication of Psoriasis, you may be referred to a doctor who specializes in arthritis (rheumatologist). You may have blood tests to rule out other conditions, such as rheumatoid arthritis, and X-rays of the affected joints may be taken. [13]

1.8 TREATMENT:

Topical treatment:

There is an array of topical and systemic drug therapies and the treatment regimens should be optimized in such way so as to achieve optimal compliance and benefit. Treatment goals for each patient is customized on the basis of concomitant comorbidities, adverse effects, existing quality of life, self-care capability, drug history, caregiver situation, financial needs and feasibility for follow up. Treatmentis usually started with the economical therapies and then escalated to newer /costlier ones until an acceptable and effective therapy is reached with good compliance. The treatment modalities are as follows

1.Corticosteroids –They are the most frequently prescribed medications for treating mild to moderate psoriasis. They slow cell turnover by suppressing the immune system, which reduces inflammation and itching. Low-potency corticosteroid ointments are usually recommended for sensitive areas such as face or skin folds, and for treating widespread

patches of damaged skin. Adverse effects seen are thinning of the skin, telangiectasia and systemic side effects such as diabetes, hypertension and HPA(Hypothalamic Pituitary adrenal) suppression. Some of the corticosteroids used are clobetasol propionate 0.05%, amcinonide 0.1%, betamethasone dipropionate, betamethasone valerate as 0.1%, 0.12% and 1%, halcinonide 0.1%, desoximetasone 0.25% and mometasone furoate

2. Vitamin D Analogues – Vitamin D analogues (Calcitriol and calcipotriene) have emerged as important alternatives to topical corticosteroids for the long term therapy of psoriasis. They bind to cytoplasmic Vitamin D Receptor then translocate into the nucleus, where they bind to nuclear receptor and commence the transcription of vitamin D responsive genes. These transcription proteins then regulate cell differentiation and down regulate cell proliferation and inflammatory processes associated with this condition. They are considered a safe alternative, despite causing perilesional irritation and erythema. They may rarely increase serum and urine calcium levels, so the total concentration per week should not exceed 210 gm. Calcitriol is more potent analogue but calcipotriene is most established one. Calcipotriene has shown to affect calcium homeostasis to very lesser extent. Most trials have shown that combination treatment of vitamin D and corticosteroid was usually more effective than monotherapy with either used alone.

3. Anthralin (Dithranol) – It is derived from the Araroba tree found in South America. It induces reactive oxygen species release, which has an inhibitory effect on hyper proliferating keratinocytes and the transformation of leucocytes. It is used in increasing concentrations (0.1% to 3%) for application to the scalp. It can be applied on in-patient basis; also, out-patient short-contact therapies are now available. Adverse effects are discoloration of the hair and skin irritation. Few studies have shown the use of anthralin when combined topical therapies or phototherapy has improved response

4.Coal Tar – It is one of the oldest topical therapies used both as monotherapy and in combination with other topical agents, systemic agents and phototherapy forthe treatment of psoriasis. The polycyclic aromatic hydrocarbons present in coal tar makes the skin more sensitive to UV(Ultraviolet) light. Still the exact mechanism of action isunclear. Coal tar has anti-inflammatory, anti-proliferative and strong anti-pruritic properties. Its unpleasant smell, staining properties and mutagenic potential has made it less compliant. In order to increase the compliance, some non-staining and washable formulations including lotions and

shampoos are available either alone orin combination with other active agent

5. Retinoid – Oral retinoid are mainly used as maintenance therapy in chronic plaque psoriasis and very specifically used in Pustular psoriasis and can also be used in Erythrodermic psoriasis but it seems to be less efficacious. It is believed to normalize DNA (Deoxyribonucleic acid) activity in skin cells and may minimize inflammation. The prescribed daily dose is 21–50 mg per day, which can be given as a single dose or in divided doses. Adverse effects of retinoid are a major concern and can include skin irritation, increased sensitivity to sunlight, xerosis, pruritus, cheilitis, alopecia, xerostomia, dyslipidemia, deranged liver enzymes and teratogenicity. A low dose regimen is also an option where up to 25 mg per day is given to minimizemucocutaneous side effects.

6. Methotrexate – This is an immune suppressive, antimetabolite and is one of the most effective as well as relatively low-cost therapy to treat psoriasis. Methotrexate is dihydrofolate reductase inhibitor and folic acid is supplemented to decrease toxicity of the drug. It is usually given as a single oral dose per week. Adverse effects can be myelosuppression, mucositis, hepatotoxicity, pulmonary toxicity, nephrotoxicity, neurotoxicity, gastrointestinal upset, nausea, oligospermia, and teratogenicity. Long term therapy can cause hepatotoxicity that can progress toliver fibrosis.

7. Cyclosporine – It is very effective oral treatment option to treat moderate- to severe psoriasis. It binds to cyclophilin, inhibits calcineurin, and hence induces immunosuppression through preventing down-stream T-cell activation. It inhibits the activation of nuclear factor of activated T-cells (NFAT) & further inhibition of gene transcription of IL-2 by T cells. Adverse effects can be nephrotoxicity, hepatotoxicity, hypertension, diabetes mellitus, neurotoxicity, hirsutism, increased risk of infection and an increase in nonmelanoma skin cancers with long-term use.

8. Phototherapy – It is recommended for those patients who do not respond to topical therapies or for patients with plaques of psoriasis covering 20% or more of the body surface. Though exact mechanism is not clear, but it is believed to induce apoptosis along with enhanced transcription and expression of IL-21 in keratinocytes. It has shown a good success rate with more than 80% of the patients having skin clearance. Ultraviolet B (UVB) radiation combined with coal tar (Goeckerman therapy) or anthralin (Ingram regimen)

has been seen to be effective in patients with moderate-to-severe psoriasis. Ultraviolet A radiation (UVA) combined with systemic psoralens (PUVA therapy) has been seen to be highly effective in clearing skin lesions, but both these therapies require a maintenance treatment and they increase the risk of skin cancer. Narrowband UVB therapy (311-313 nm) is more effective than broadband UVB treatment. It is administered2 to 3 times a week until the skin improves, then maintenance may require only weekly sessions. It may cause more severe and longer lasting burns. When given in combination with topical tazarotene, it is almost equally efficacious and safer alternative to PUVA. Adverse effects are redness, itching, dry skin, wrinkled skin, freckles & skin cancer.

NEW DRUG TARGETS- In the past two decades the interest has shifted towards the pathogenesis-based treatment which has led to development of novel biologics. These therapies aim at providing more selective, immunologically directed intervention, with a hope that such specificity will result in fewer side effects than traditional therapies. As this is an era of target-based therapies, the development of the new drugs and biologics are based on following strategies:
Blockade of initial cytokine release and APC (Antigen presenting cells) migration

- Targeting activated T cells and prevent further T-cell activation and immunological cascade
- Inhibition of cytokines such as TNF-a
- Inhibition of differentiation of the activated T cells into Th1 and Th17 cells
- Inhibition of cytokines like IL-17 and its interaction with the receptor

Biologics:
These are the molecules, which are developed for target-based therapy. They have a more precise action and side effects are thought to be less as compared to the broad traditional therapies. These agents act on the varied steps of the pathogenesis of the psoriasis and are divided into various groups on the basis of their mode of action. ANTI TNF-α AGENTS These are molecules, which act on the tumor necrosis factor (TNF-a) or by blocking the TNF-a receptors. Psoriatic plaques contain a high amount of TNF-a which is a strong pro-inflammatory cytokine andis one of the prime mediators in the development of inflammation in psoriasis. TNF-a stimulates the production of other cytokines, activates other immune cells

and increases its own secretion and also induces the adhesion of molecules by keratinocytes and further increases the recruitment of immune cells.

Hence, anti TNF-a agents binds to TNF-a, captures them and finally neutralizes them or blocks the TNF-a receptor on the keratinocytes and other immune cells to shut down the immunological cascade. The first biologic in this group is Infliximab. Other anti TNF-a agents which have been developed till now are Etanercept, Certolizumab pegol, Adalimumab, Golimumab

Infliximab is a chimeric monoclonal antibody prepared by joining human immunoglobulin (IgG1) constant region to a murine-derived antigen-binding variable region. Infliximab has high affinity for both soluble and trans membrane-bound forms of TNF-a and hence inhibits the ability of TNF-a to bind to its receptors and initiate the intracellular signaling, which further leads to gene

transcription and subsequent inflammatory cascade. The recommended dosage is 5 mg/kg body weight as IV infusion at 0, 2 and 6 weeks followed by every 8 weeks thereafter. First three infusions are to be given under supervision, as there are high chances of infusion reactions. Other adverse effects can be development of anti- nuclear antibody and rarely, a lupus like syndrome. It is also approved for indications like rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis (UC), and ankylosing spondylitis (AS).

Etanercept is a recombinant human TNF-a receptor fusion protein which neutralizes soluble TNF-a and is in the use for moderate to severe psoriasis. Recommended dosage is 50 mg subcutaneously twice weekly for the first three months and thereafter followed by 50 mg weekly. Contraindications to therapy are multiple sclerosis, congestive heart failure (CHF), immunosuppression, hepatitis B. It is also approved for RA. Certolizumab pegol is a recombinant, humanized anti-TNF-a antibody. It is administered subcutaneously as 400 mg taken at week 0, week 2, week 4, then every 2 weeks thereafter.

Adverse are CHF, lupus like syndrome, hepatitis B reactivation, easy bruising.

IL-23 AND IL- 12 INHIBITORS

Th17 cells and IL-23 are important in the pathogenesis of psoriasis. IL-23 stimulates the immune cells and increases their proliferation and survival. Dendritic cells and macrophages increase the production of IL23 and are important for the development and maintenance of Th17 cells. These IL-23 and IL-12 inhibitors like Ustekinumab and Apilimod block the

subunits of IL-23 and IL-12 and hence ceases the immunological cascade.

Ustekinumab – It is a humanized monoclonal antibody directed against p40, a subunit of IL-23 and IL-12 and inhibits their signal-transduction pathways that normally promote the differentiation of naive T cells into Th1 and Th17 cells respectively. The treatment is started with 45mg (or 90mg if >210kg) at weeks 0and 4 and every 12 weeks thereafter. The clinical trial data shows a comparable PASI response of adalimumab and ustekinumab and a head-to-head study with etanercept showed a more favorable PASI response of ustekinumab compared to etanercept. It has been recently approved for Crohn's disease.

Guselkumab – It is a human monoclonal IgG1a antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. It has shown to reduce serum levels of IL-17A, IL-17F and IL-22 relative to pre- treatment levels in evaluated subjects with psoriasis. The recommended dose is subcutaneous injection of 210 mg at Week 0, Week 4, and every 8 weeks thereafter. This biologic has been approved this year for the treatment of adults with moderate-to-severe plaque psoriasis.

IL-17 A RECEPTOR INHIBITOR

Brodalumab is a monoclonal antibody that targets interleukin-17RA, blocks signaling of interleukins 17A and 17F and also the interleukin-17A/F heterodimer, hence blocking the downstream pathways, all of which play a role in the inflammatory cascade of psoriasis. Recently FDA approved brodalumab for treatment of moderateto-severe plaque psoriasis. The week 12 PASI 210 response rates were significantly higher with 221 mg of brodalumab than with ustekinumab but neutropenia was higher than with ustekinumab. A dose of 221 mg is administered by subcutaneous injection at weeks 0, 1, and 2 followed by 221 mg every 2 weeks. FDA has issued warning regarding increased risk of suicidal ideation and behavior

FUSION PROTEIN INHIBITOR

Alefacept is the drug in this group, which is approved by FDA. It is a human fusion protein and it binds to CD2 on T cells. It has dual mechanism of action; it blocks the interaction between the leukocyte-function associated antigen (LFA)-3 and CD2 on T cells and hence blocks the activation and proliferation of theimmune CD4+ and CD8+ T cells. It also induces apoptosis of activated memory T cell.58 Dosage is 15 mg IM or 7.5 mg IV per

week and adverse effects can be lymphopenia, skin cancers, lymphomas, hepatotoxicity.

JANUS KINASE (JAK) INHIBITOR

Tofacitinib is an oral selective Janus kinase inhibitor that was approved by FDA for the treatment of rheumatoid arthritis (RA) but recently it is being studied and is in phase 3 trials for the treatment of psoriasis

PHOSPHODIESTERASE-4 INHIBITOR

Phosphodiesterase 4 (PDE4) is an enzyme that is responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP), which is an intracellular second messenger that controls a group of pro-inflammatory and anti-inflammatory mediators. [14]

ALTERNATIVE TREATMENT OF PSORIASIS:

A thorough survey of literature revealed that a number of plants such as Aloe vera, Centella asiatica, Panax ginseng, Rubia cordifolia, Saccharum officinarum, etc. have been reported to exhibit antipsoriatic activity.

- Aloe vera (L.) Burm. (Liliaceae) Ghritakumari

  Extract of leaves (0.5%) in hydrophilic cream

  Topical; three times daily for five consecutive days per week (4 weeks)
- Angelica dahurica Fisch. ex Hoffm. (Apiaceae) Bai Zhi/ root of the holy ghost Aqueous extract of roots

  Topical, followed by UV-A exposure
- Betula alleghaniensis Britt. (Betulaceae)

  Yellow birch Polyphenolic extract of bark

  In vitro; 24 and 48 h exposure Normal human keratinocytes (NHK) and psoriatic keratinocytes (PK)
- Caesalpinia bonduc (L.) Roxb. (Caesalpiniaceae)
- Celastrus orbiculatus Thunb. (Celastraceae)
- Centella asiatica (Apiaceae)
- Coptis chinensis (Ranunculaceae)
- Eruca sativa Mill. (Brassicaceae)
- Mahonia aquifolium Rubisan (Berberidaceae)
- Panax ginseng C.A. Meyer (Araliaceae) [15]

1.9 SCREENING METHODS:

- **Spontaneous mutations:** Spontaneous mutations in mice were the first animal models in which certain genetic backgrounds and allelic mutations resulted in a psoriasis-like Psoriasis. Prominent examples of spontaneous mutations are Asebia (Ab), chronic proliferative Psoriasis, flaky tail, and flaky skin (Fsn) mice. Ab mice were used as one of the first in vivo models of hyperkeratosis They display moderate epidermal acanthosis and increased dermal vascularity, macrophages, and mast cells. Chronic inflammatory skin changes are somewhat more pronounced in flaky tail mice, albeit at variable levels.
- **Genetically engineered animals** Psoriasis is a multifactorial disorder. Interactions of different genetic susceptibility loci and gene products respectively, contribute to the accrual and the course of the disease. This notion is exemplified by the tumor necrosis factor (TNF), which are associated with a decreased or increased risk of psoriasis, respectively.

- **The IL-23/IL-17 axis in the pathophysiology of psoriasis and in animal models** Several cytokines and their receptors are encoded by psoriasis-associated genes. These include IL-12B, IL-23A, and IL-23 receptor. In mice, intradermal injection of IL-23 results in a TNF-a– and IL-20R2–dependent psoriasis-like inflammatory response.

- **IL-36 in the pathophysiology of psoriasis and in animal models** Abnormal IL-36 signaling or loss-of-function mutations in IL36RN play major roles in the formation of pustular psoriasis. The involvement of IL-36 in pustular psoriasis was first suggested by a missense mutation in IL-36RN in humans. Similar to human psoriasis, mice overexpressing IL-36a in basal keratinocytes under a K14 promoter Keratinocyte Interleukin-36 K14/IL-36(transgenic mice) showed epidermal thickening and immune cell infiltration. [16]

- **Ultraviolet radiation:**

  Ultraviolet ray B (UV-B) induced Psoriasis in the rat may be a model for human psoriasis vulgaris. Rat skin responded to UV-B irradiation quite differently from human, guinea-pig, or mouse skin. Rat UV-B Psoriasis was characterized by a sharply demarcated brownish-red lesion with scale formation lasting for 21 days. Histopathologically,

microvascular dilatation, intraepidermal accumulation of polymorphonuclear leucocytes with microabscess, mononuclear cell infiltration at the papillary dermis and hyperproliferation of epidermal cells occurs. These features were similar to those of clinical psoriasis vulgaris in man. Leucocyte suppression, induced by systemic ferritin administration to the irradiated rats, resulted in loss of the epidermal hyperproliferation and inhibition of the tissue leucocytosis.This leucocyte suppression remodelled the rat UV-B Psoriasis into that seen in other mammalian species, where microvascular dilatation and degeneration of keratinocytes (so-called sunburn cells) are characteristic. The irradiated epidermis of the rats treated with ferritin possessed an in vitro PMN (Polymorphonuclear leukocytes) chemotactic property. Rat UV-B Psoriasis seems to be a useful model to investigate aetiopathogenic mechanisms in psoriasis vulgaris. [17]

5% w/w Imiquimod cream

- Topical application of imiquimod (IMQ), a TLR7/8(Toll Like Resceptor) ligand and potent immune activator, can induce and exacerbate psoriasis, a chronic inflammatory skin disorder. Recently, a crucial role was proposed for the IL-23/IL-17 axis in psoriasis. Daily application of IMQ on mouse back skin induced inflamed scaly skin lesions resembling plaque type psoriasis. These lesions showed increased epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis, and infiltrates consisting of $CD4^+$ T cells, $CD11c^+$ dendritic cells, and Plasmacytoid dendritic cells. IMQ induced epidermal expression of IL-23, IL-17A, and IL-17F, as well as an increase in splenic Th17 cells. IMQ-induced Psoriasis was partially dependent on the presence of T cells, whereas disease development was almost completely blocked in mice deficient for IL-23 or the IL-17 receptor, demonstrating a pivotal role of the IL-23/IL-17 axis. In conclusion, the sole application of the innate TLR7/8 ligand IMQ rapidly induces a Psoriasis closely resembling human psoriasis, critically dependent on the IL-23/IL-17 axis. This rapid and convenient model allows further elucidation of pathogenic mechanisms and evaluation of new therapies in psoriasis. [18]

PLANT PROFILE

2. PLANT PROFILE:

Zingiber officinale roscae root belongs to the family of zingiberaceae.

Synonym:

Zingiber officinale var. *rubens* Makino

2.1 BOTANICAL CLASSIFICATION

Domain: Eukaryota

Kingdom: Plantae

Phylum: Spermatophyta

Subphylum: Angiosperms

Class: Monocotyledon

Order: Zingiberales

Family: Zingiberacea

Genus: Ginger

Species: Zingiber officinale

Botanical name:

Zingiber officinale roscae

2.2 VERNACULAR NAME:

Tamil name: Inji

Malayalam name: Inchi

Telugu: Allam

Kannada: Shunti

COMMON NAME: cooking stem, canton[19]

PLANT PICTURE:

Fig no: 5 Plant of *Zingiber officinale roscae*

Fig no: 6 Root of *Zingiber officinale roscae*[20]

2.3 HISTORICAL BACKGROUND

It has been used as a spice and medicine in India and China since ancient times. It was the first oriental spice known in Europe and having been obtained by the Greeks and Romans from Arab traders, who kept a secret of their origin of the spice in India. It was known to Discorides and Pliny in the first century A. D., the former frequently refers to it in his De Materia Medica describing its warming effects on the stomach and as an aid to digestion and antidote to poisons. The Sanskrit name Singhabera give rise to Green Lingiberi and later Latin Lingiber. It is mentioned in Koran. In Arabian nights it has been referred for its

aphrodisiac properties. India enjoys from times immemorial a unique position in the production and export of ginger. Ginger was originated in Southern China. On world level, it grows in Jamaica, Nigeria, China, Taiwan, Australia, Japan etc. In India, it is grown in the states like Kerala, North Eastern States, Sikkim, Himachal Pradesh, Odisha, West Bengal, Karnataka, Andhra Pradesh and Maharashtra.

2.4 COMPOSITION

Ginger contains up to 3% of an essential oil that causes the fragrance of the spice. The main constituents are sesquiterpenoids with –zingiberene as main component. Lesser amounts of other sesquiterpenoids and small monoterpenoid fraction have also been identified. The pungent taste of gingers due to non-volatile phenyl propanoic and diarylheptanoids; latter are more pungent and form from the former when ginger is dried. Cooking ginger transforms gingerol into zingerone, which is less pungent and has a spicy-sweet aroma. None of these pungent chemicals are related to capsaicin, the principal hot constituent of Chile pepper [(20)]

2.5 CHEMICAL CONSTITUENTS

Volatile Oils: Volatile oils, also known as ginger essential oils, are generally composed of terpenoids. Ginger essential oils give *Zingiber officinale roscae* a unique aromatic smell volatile oil composition varies based on where the *Zingiber officinale roscae* is harvested.

Gingerol: Gingerol is the spicy component of *Zingiber officinale roscae*. It is a mixture of various substances, all of which contain the 3- methoxy-4-hydroxyphenyl functional group. Gingerols can be divided into gingerols, shogaols, paradols, zingerones, gingerdiones, and gingerdiols, according to the different fatty chains connected by this functional group

Diarylheptanoids: Diarylheptanoid is a group of compounds with 1,7-disubstituted phenyl groups and heptane skeletons in its parent structure. Currently, it can be divided into linear diphenyl heptane and cyclic diphenyl heptane compounds with antioxidant activity

Proteins and Amino Acids. *Zingiber officinale roscae* contains a variety of amino acids, including glutamate, aspartic acid, serine, glycine, threonine, alanine, cystine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, lysine, histidine, arginine, proline and tryptophan

Sugars: *Zingiber officinale roscae* also contains polysaccharide, cellulose, and soluble sugar

Organic Acids: *Zingiber officinale roscae* contains oxalic acid, tartaric acid, lactic acid, acetic acid, citric acid, succinic acid, formic acid, and malonic acid

Inorganic Elements: *Zingiber officinale roscae* has been shown to contain more than 20 inorganic elements such as K, Mg, Ga, Mn, P, Al, Zn, Fe, and Ba [(21)]

2.6 USES

Cardiovascular health: Including in Ayurvedic science, ginger has been described as great heart tonic. It helps in preventing various heart diseases by reducing blood clotting that can lead to plaque formation or thrombosis. It can also open the blockage in the blood vessels thus decreasing peripheral vascular resistance and hence blood pressure. Ginger also may help to lower high cholesterol making the heart healthy

Antiplatelet activity: found that aqueous extract of ginger inhibited platelet aggregation induced by ADP (Adenosine diphosphate), epinephrine, collagen and arachidonic acid in vitro. Ginger acted by inhibiting thromboxane synthesis. It also inhibited prostacyclin synthesis in rat aorta. The antiplatelet action of 6-gingerol was also mainly due to the inhibition of thromboxane formation

Powerful antioxidant: Antioxidant helps to prevent all kind of disease and it also slower downs the aging process. There was a study of more than 120 plant foods, published in the Journal of Nutrition. In the report ginger was ranked number one among the five richest food sources of antioxidants, including berries, walnuts, sunflower seeds, and pomegranates. Test-tube and animal researches have shown that ginger inhibits the production of free radicals. Ginger also enhances the body's internal production of antioxidants

Help for cancer patients The only therapy available for cancer is chemotherapy. The side effects of any chemotherapy include nausea and hair fall. Ginger can reduce nausea that is occurring as a major side effect from chemotherapy treatment. In addition, test-tube studies have shown that some favorable qualities found in ginger can even offer some protection against cancer cells

Inflammation: Ginger constituents inhibit arachidonic acid metabolism and thus prostaglandin synthesis. This may account for some of its anti-inflammatory properties. One constituent specifically, (6)-Shogaol, (found in semi-dry, but rarely fresh ginger), appears to interfere with the arachidonic / inflammatory cascade. It is found to inhibits cyclooxygenases and prevents specific prostaglandin release in rabbits and rats. Ginger may be a stronger inhibitor of prostaglandin synthesis than indomethacin. It can be used either for rheumatoid or osteoarthritis. Ginger extract is anti-inflammatory on osteoarthritic sow cartilage in vitro (22)

LITERATURE REVIEW

3. LITERATURE REVIEW

ANTI DIABETIC ACTIVITY

Zainab M Al-Amin et al (Oct 2006) reported the hypoglycemic effect of ginger (*Zingiber officinale*). An aqueous extract of raw ginger was administered daily for a period of 7 weeks to streptozotocin (STZ)-induced diabetic rats. Results revealed that, raw ginger possesses hypoglycemic, hypocholesterolemia and hypolipidemic activity. [23]

ANTI-HYPERLIPIDEMIC AND HYPOTHYROIDISM ACTIVITY:

Ahmad Sameer Al-Noory, et al (2019) reported effect of fresh ginger extracts *Zingiber officinale roscoe* on serum lipid profile and on blood glucose in alloxan-induced diabetes and propylthiouracil-induced hypothyroidism in rats. [24]

ANTI- INFLAMMATORY:

Ndanusa Abdullah hassan, et al (2016) reported anti-inflammatory effect of aqueous extract of *Zingiber officinale* on carrageenan-induced inflammation on Sprague Dawley (SD) rats. The paw edema in carrageenan-induced SD rats was considerably reduced by treating ginger extracts when compared to the untreated SD rats. [25]

NEUROLOGICAL DISORDER:

Jin Gyu Choi et al (Feb 2018) reported 6-gingerol, 6-shogaol, 6-paradol, zingerone, and dehydrozingerone, are effective in ameliorating the neurological symptoms and pathological conditions through by modulating cell death or cell survival signaling molecules.[26]

ANTI-ULCER ACTIVITY:

Jun-Kyu Shin et al (Oct 2020) reported antiulcer activity of steamed ginger extract against ethanol (EtOH)/HCl-induced gastric ulcers in a rat model. Ginger extract were orally administered for 14 days Results revealed ginger extract possesses antiulcer activity by attenuating oxidative stress and inflammatory responses. [27]

CARCINOGENIC ACTIVITY:

Sahdeo Prasad et al (2015) reported the anticancer activity of ginger is attributed to its ability to modulate several signaling molecules like NF-κB, STAT3, MAPK, PI3K, ERK1/2, Akt, TNF-α, COX-2, cyclin D1, cdk, MMP-9, survivin, cIAP-1, XIAP, Bcl-2, caspases.[28]

HEPATOTOXICITY:

Abdelgawad Fahmi et al (jul 2019) reported the hepatoprotective effect of dry *Zingiber officinale* (ginger) and its essential (volatile) oil against diethylnitrosamine (DEN) toxicity in rats. Antioxidant activity was determined *in vitro* and reported that Ginger was able to reduce the severity of DEN-cytotoxicity in rats [29]

ANTI-DIARRHOEAL ACTIVITY:

Changrong Zhang, et al (2020) reported the effect of ginger on visceral pain, and possible underlying mechanism by which ginger is used to relieve IBS-D (irritable bowel syndrome with diarrhoea) intestinal hypersensitivity. [30]

WOUND HEALING:

Narasimharao Bhagavathula, et al (2009) reported that rats were topically treated with combination of curcumin and ginger extract for 21 days. Following this rat were treated with temovate for 15 days followed by superficial abrasion wounds were induced in the treated skin. Healing was more rapid in combination of curcumin and ginger extract than the temovate and control rat. [31]

ANTI-MICROBIAL ACTIVITY:

Arshad H Rahmani, et al (2014) reported ginger and its constituents showed significant role in the prevention of diseases via modulation of genetic and metabolic activities. Therapeutic effects of ginger and its constituents in the diseases management, and its impact on genetic and metabolic activities. [32]

MENUSTRAL CRAMPS:

Parvin Rahnama, et al (2012) reported effects of ginger on pain relief in primary dysmenorrhea. it was a randomized, controlled trial. The study was based on a sample of one

hundred and twenty students with moderate or severe primary dysmenorrhea. They were randomly assigned into two equal groups, one for ginger and the other for placebo in two different treatment protocols with monthly intervals. The ginger and placebo groups in both protocols receive ginger root powder or placebo three times a day. In the first protocol ginger and placebo were given two days before the onset of the menstrual period and continued through the first three days of the menstrual period. In the second protocol ginger and placebo were given only for the first three days of the menstrual period. Severity of pain was determined by a verbal multidimensional scoring system and a visual analogue scale and reported that there was a significant difference in the severity of pain between ginger and placebo groups for protocol. [33]

NAUSEA AND VOMITTING:

Iñaki Lete et al (2016) reported that Various preclinical and clinical studies have evaluated ginger as an effective and safe treatment for nausea and vomiting in the context of pregnancy and as an adjuvant treatment for chemotherapy-induced nausea and vomiting. [34]

CNS ACTIVITY:

Pradeep Kumar Sharma et al (2016) reported potential pharmacological effects of ethanolic extracts of *Z. Officinale* with respect to central nervous system (CNS) activity in mice. Ginger extract exhibited anxiolytic activity increased the sleeping latency but reduced the sleeping time. [35]

ANTIOXIDANT ACTIVITY:

Kwanjit Danwilai, et al (2017) reported that antioxidant activity of ginger extract oral supplement in newly diagnosed cancer patients receiving adjuvant chemotherapy compared to placebo. Daily supplement of ginger extract started 3 days prior to chemotherapy has significantly elevate antioxidant activity. [36]

OSTEOARTHRITIS:

E.M.Bartels et al (2015) reported that clinical efficacy and safety of oral ginger for symptomatic treatment of osteoarthritis (OA) Randomized controlled trials (RCTs) comparing oral ginger treatment with placebo in OA patients aged >18 years. And reported that reduction in pain and reduction in disability. [37]

MEMORY IMPAIRMENT:

AliGomar et al (2014) reported that chronic treatment with hydroethanolic extract of ginger would effect on the passive avoidance learning (PAL) and memory in rat. Administration of extract in morphine received animal groups before retention trials also increased the time latency than the morphine-treated group. So, they reported that ginger extract attenuated morphine induced memory impairment. [38]

MIGRAINE:

LiyanChen et al (2021) reported that randomized controlled trials (RCTs) assessing the effect of ginger versus placebo on treatment efficacy in migraine patients. This meta-analysis is performed using the random-effect model. RCT has been compared with control group in migraine patients, ginger treatment is associated with substantially improved pain free at 2 h and the incidence of nausea and vomiting is obviously lower in ginger group than that in control group. [39]

NEPHROPROTECTIVE ACTIVITY:

Ayodele Jacob Akinyemi et al (2019) reported that cadmium (Cd) induces nephrotoxicity and Nephroprotective effect of essential oils from Nigeria ginger and turmeric rhizomes in cadmium-treated rats by examining their effect on renal function biomarkers. Essential oils from ginger and turmeric rhizomes exert anti-inflammatory effect. [40]

SCOPE OF WORK

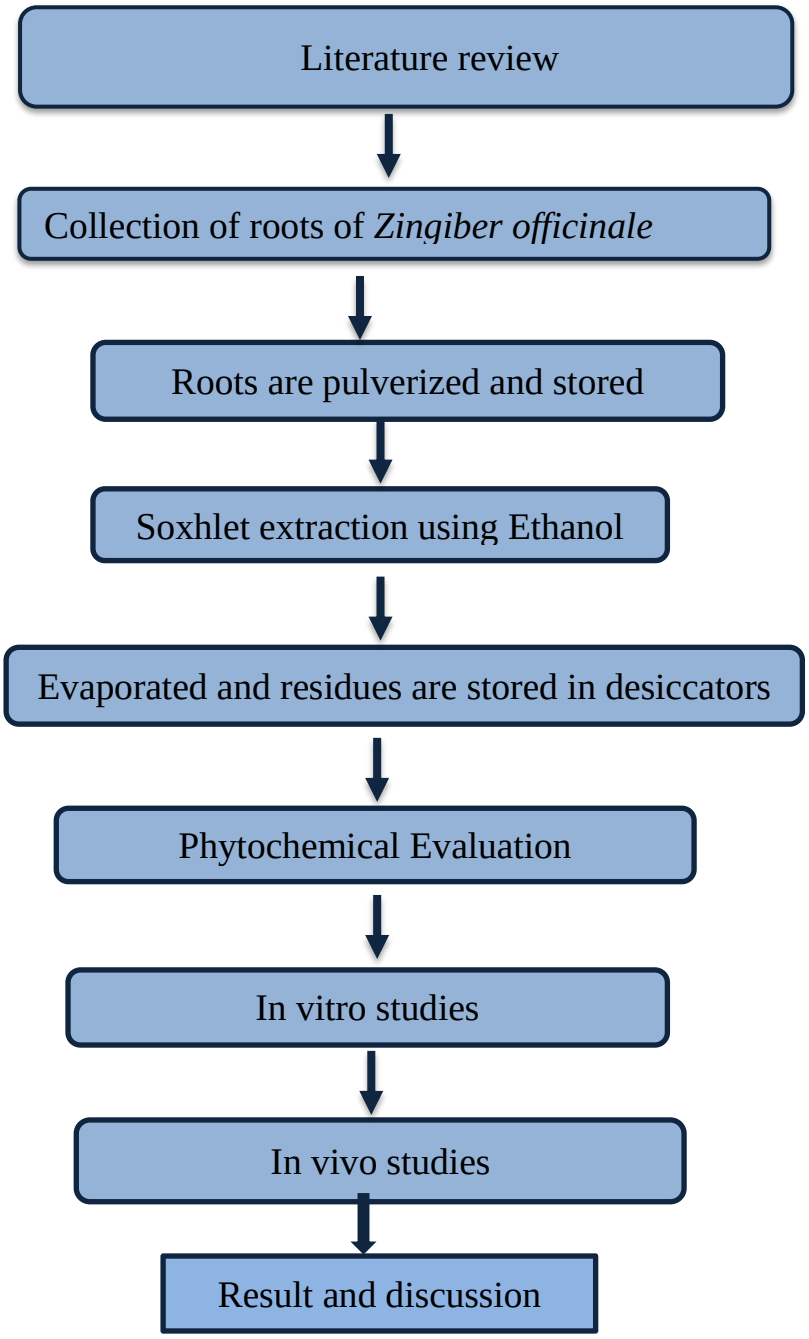
4. SCOPE OF WORK

Psoriasis is a chronic, non-communicable, painful, disfiguring and disabling disease for which there is no cure and with great negative impact on patients. The adverse effect are Scaling, Redness, Erythema, and increase in inflammatory mediators such as Interleukin-23 The Present work is to evaluate the effect of *Zingiber officinale roscae* gel for management of Psoriasis and to give safe and effective treatment. Medicines dervived from natural sources are known as phytomedicines which are clinically safe and effective due to lesser number of side effects and effective therapeutic index. Thus, the demand for use of herbal medicines have been increased now a days.

The objective of this study is to evaluate the Anti-Psoriatic Activity of *Zingiber officinale roscae* gel in UV-Radiation and 5% Imiquimod induced Psoriasis in Wiatar rats.

PLAN OF WORK

5. PLAN OF WORK:



MATERIALS AND METHODS

6. MATERIALS AND METHODS

6.1 COLLECTION OF PLANT MATERIAL:

Fresh Roots of *Zingiber officinale roscae* Were collected from local market in Parrys (chennai) and authenticated from Prof.P.Jayaraman, Ph.D,Director, Institute of herbal botany, Zingiber officinale roscae anatomy and research centre, Chennai, Tamilnadu, India. A Copy of authentification certificate is attached in Annexure

6.2 CONTINOUS SOXHLET EXTRACTION

The preparation of various extracts of *Zingiber officinale roscae* root was done in the Department of Pharmacology, C.L Baid Metha college of Pharmacy,
Chennai-97. The apparatus used for continuous hot percolation process was Soxhlet apparatus which consist of three parts:

1. Round bottom flask containing the boiling solvent
2. Soxhlet extractor in which the drug to be extracted is packed. It has a side tube which carries the vapours of the solvent from the flask to be condenser and a siphon tube which siphons over the extract from Soxhlet extractor to the flask.
3. A condenser in which the vapour of the solvent are condensed to solvent

Procedure: The finely divided powder of the *Zingiber officinale roscae* root was placed inside a thimble made from thick filter paper, which was loaded into the main chamber of the Soxhlet extractor. The Soxhlet extractor was placed onto a flask containing the extraction solvent Ethanol Soxhlet was then equipped with a condenser with an inlet and outlet. The fluid was heated to reflux. The vapour travels up the distillation arm and floods into the chamber housing the thimble of solid material. The condenser ensures that any vapour that cools drips back down into the chamber housing the solid material. The chamber containing the powder slowly fills with warm solvent. Some of the desired compound will then dissolve in the warm solvent. When the Soxhlet chamber is almost full, the chamber is automatically emptied by a siphon side arm, with the solvent running back down to the distillation flask. This cycle was allowed to repeat many times, over 5-6 hours for 4 days. During each cycle, a portion of the non –volatile component dissolves in the solvent. After many cycles the desired compound is concentrated in the distillation flask. After extraction the solvent is removed, typically by means of a rotary evaporator, yielding the extracted compound. The

non –soluble portion of the extracted solid remains in the thimble, and was discarded. The roots of *Zingiber officinale roscae* were dried, powdered and subjected to successive extraction by Soxhlet apparatus using ethanol as solvents. After the extraction the products were concentrated by using rotary evaporator by removing solvents. Then the extracts were dried and stored in a suitable air tight container. The extracts can
used whenever they required. [41]

Percentage yield:

The percentage yield of Ethanolic extract was 12% w/w and it was preserved in refrigeration for further use.

6.3 PREMILINARY PHYTOCHEMICAL SCREENING:

Qualitative Phytochemical Screening of Ginger and Extracts

Phytochemical screening was carried out ethanol, chloroform, ethyl acetate, acetone and water extracts of ginger and using standard procedures

Test for tannin [42]

0.5 g of *Zingiber officinale roscae* extract was mixed with 2ml of water and heated on water bath. The mixture was filtered and 1ml of 21% Ferric chloride solution was added to the filtrate. A blue-black solution indicates the presence of tannin.

Test for flavonoid [42]

5 ml of distilled water and about 0.2 g of *Zingiber officinale roscae* extract were mixed thoroughly. And 1 ml of 1% Aluminium chloride solution was added and shaken. A light yellow precipitate indicates the presence of flavonoids.

Test for phenol [42]

About 0.5 g of *Zingiber officinale roscae* extract was added to 1 ml of 21% Ferric chloride solution. A deep bluish green Colouration was an indication for the presence of phenol.

Test for saponin [42]

About 0.2 g of *Zingiber officinale roscae* extract was shaken with 4 ml of distilled

water and then heated to boil on a water bath. Appearance of creamy miss of small bubbles (Frothing) shows the presence of saponin.

Test for ascorbic acid [42]

About 0.5 g of *Zingiber officinale roscae* extract was added to 2 ml of acetic acid and it was shaken for 3 minutes, and then filtered. Few drops of 2, 6-Dichlorophenolinddophenol solution were added to the filtrate. The presence of faint pink colour confirms that ascorbic acid is present.

Test for reducing sugar [42]

2 ml of distilled water and 0.2 g of *Zingiber officinale roscae* extract were mixed together and thoroughly shaken in a test tube. 1 ml each of Fehling solution A and B were added to the mixture. A brick-red precipitate at the bottom of the test tube confirms the presence of reducing sugar

Test for resin [42]

0.2 g of *Zingiber officinale roscae* extract and 2 ml of acetic anhydride were mixed together. A drop of concentrated sulphuric acid was added to the mixture. A purple or violet colour indicate the presence of resin.

Test for balsams [42]

0.2 g of *Zingiber officinale roscae* extract and 2 ml of ethanol were mixed together and two drops of alcoholic ferric chloride solution was added. A dark green colouration indicates the presence of balsams

Test for chalcone [42]

0.2 g of *Zingiber officinale roscae* extract and 2 ml of 1% ammonium hydroxide were mixed together. The appearance of reddish colour shows the presence of chalcone.

Test for glycoside [42]

0.2 g of *Zingiber officinale roscae* extract and 2.5 ml of dilute sulphuric acid were mixed together and boiled for 15 minutes, cooled and neutralized with 5 ml each of Fehling solution A and B. The formation of brick red precipitate confirmed glycoside

Acidic test [42]

0.2 g of *Zingiber officinale roscae* extract and sufficient distilled water were mixed together and warmed on hot water bath and cooled. A wet litmus paper was dipped inside the solution

Test for volatile oil [42]

0.2 g of *Zingiber officinale roscae* extract and 2 ml of ethanol were mixed together and few drops of ferric chloride solution was added. A green colouration indicates volatile oil. **[42]**

Test for amino acid (protein) [42]

0.2 g of *Zingiber officinale roscae* extract and 5 ml of distilled water were mixed together and left for 3 h. The mixture was later filtered. To 2 ml of the filtrate, 0.1 ml million reagent was added. A yellow precipitate indicates the presence of protein (amino acid)

Test for Phlobatannins [42]

0.2 g of *Zingiber officinale roscae* extract and 2 ml of 21% aqueous hydrochloric acid solution were mixed together and boiled. A deposition of red precipitate indicates the presence of phlobatannins.

Test for anthraquinones[42]

0.2 g of *Zingiber officinale roscae* extract and 5 ml of chloroform were mixed, shaken together for 5 minutes. The mixture was filtered. 2.5 ml of 21% ammonium hydroxide was added to the filtrate. A bright pink, red or violet colour at the upper layer indicates free anthraquinones.

Test for steroids (Salkowski test) [42]

0.2 g of *Zingiber officinale roscae* extract and 2 ml of chloroform were added together, 2 ml of concentrated sulphuric acid was added to form a layer. The formation of a violet/blue/green/reddish-brown ring at the interface indicates the presence of steroidal ring.

Test for Gums and Mucilage: [42]

0.2g of extract was treated with 25ml of absolute alcohol and then solution was filtered. The filterate was examined for its Swelling properties

6.4 PREPARATION 1% AND 5% of *Zingiber officinale roscae* GEL:

Making a gel base: The base is made by dispersing Hydroxy propyl methyl cellulose with 60 ml of distilled water, pouring the distilled water gradually and
increasing the volume with the remaining 60 ml of distilled water the homogenized.

Gel Making: Making ginger root extract gel (*Zingiber officinale roscae*) with a concentration of 1% is made by dispersing HPMC(Hydroxy Propyl Methyl Cellulose) with 60 ml of distilled water, which has been added with sodium benzoate, stirring until homogeneous, adding the remaining 650 ml distilled water. Then stored in the first container. The gel preparation of ginger rhizome extract (*Zingiber officinale roscae*) with a concentration of 5% was made in the same manner as at a concentration of 1%, where HPMC was dispersed with 60 ml of distilled water, stirred until homogeneous, then stored in the first container. Then in the second container, the ginger extract (*Zingiber officinale roscae*) is dispersed in glycerin, propylenglycol and triethanolamine until homogeneous, enter the base contained in the first container into the second container and homogenize it.

ACUTE TOXICITY STUDY:

Acute toxicity studies for *Zingiber officinale roscae* was performed and it was found to be safe Hence the dose selected for the study was 1% gel (Low dose) and 5% gel (High dose)

6.5 EVALUATION OF GEL:

Stability test: It includes organoleptic test such as smell, consistency, color and shape of Prepared 1% and 5% of gel and the result was found to be

Scent: Unique

Consistency: Thick

Color: Yellow

Form: Gel [43]

PH of the gel preparation: The gel was tested by PH paper. And PH of both 1% and 5% of gel was found to be 6. [43]

Spreadability test: The test procedure was carried out by using 1 g of gel in the middle of the tool with a diameter of 15 cm, the one glass was left on it for 1 minute, then the measured gel diameter was put 50 g additional load, let stand for 1 minute and measured the diameter

of the gel that spreads. This was repeated until a significant diameter was obtained, and the concentration of 1% with a sample weight of 1 gram resulted 0 to 5cm, and a concentration of 5% with a sample weight of 1 gram the results are 0 to 5cm .Normally test results of good gel dispersion between 5-7 cm[43]

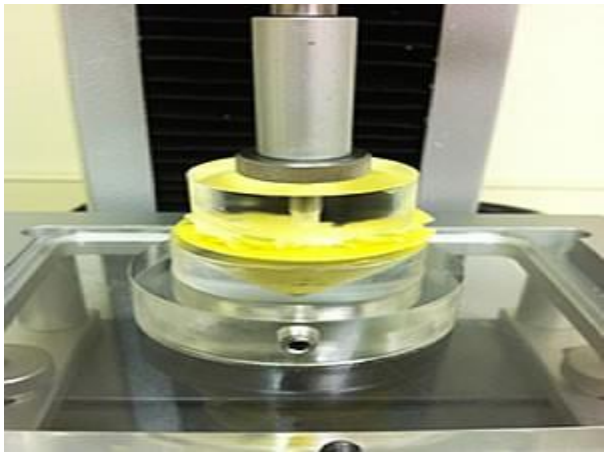


Fig no 7: Spreadability test apparatus

7. ANIMAL STUDY:

Study centre:

The study was carried out in the Department of Pharmacology and animal house, C.L Baid Metha college of Pharmacy, Chennai-97.

7.1 PROCUREMENT OF ANIMALS: The present study was conducted after obtained approval from the Institutional Animal Ethics Committee 06/321/PO/Re/S/01/CPCSEA, C.L Baid Metha college of Pharmacy, Chennai-97. The protocol met the requirements of national guidelines of CPCSEA Thirty Male Wistar Rats were procured from the animal house C.L Baid Metha college of Pharmacy, Chennai 97. The animals were maintained under standard laboratory conditions, [temperature (25±1) ^{o}c, relative humidity 55%-65% and normal day/dark circle period [12hr dark/12 hr. light] All the animals included in the study were given standard laboratory feed and water ad libitum. The animals were allowed to acclimatize in the laboratory for one week.

DRUGS AND CHEMICALS

Tretinoin Microsphere gel 0.04% w/w – Sigma Aldrich Mumbai
Clobetasol propionate cream 0.05% w/w-– Sigma Aldrich Mumbai
Imiquimod cream 5% w/w– Sigma Aldrich Mumbai

INVIVO AND INVITRO ANTI-PSORIATIC STUDY

7.2 INVIVO:

7.2.1 ULTRAVIOLET RADIATION INDUCED PSORIASIS IN WISTAR RATS.

Chemicals:

Inducing agent: Ultraviolet radiation at 365nm for 30 mins.

Experimental procedure:

The Wistar Rat was divided into five groups of six each. Hairs on the dorsal skin was removed Group I treated as normal control. Group II treated with Ultraviolet radiation at 365nm for 30 mins into a dorsal surface of skin for five days. Group III treated with Ultraviolet radiation at 365nm for 30mins into a dorsal surface of skin for five days then treated with Tretinoin gel 0.04%w/w (positive standard) 12.5mg/cm^2(Topically) from sixth to twenty first day. The Group IV treated with Ultraviolet radiation at 365nm for 30 mins into a dorsal surface of skin for five days. Then treated with *Zingiber officinale roscae* gel 1% (low dose of test drug) 12.5mg/cm^2 (Topically) from sixth to twenty first day. The Group V treated with Ultraviolet radiation at 365nm for 30mins into a dorsal surface of skin for five days then treated with *Zingiber officinale roscae* gel 5% (high dose of test drug) 12.5mg/cm^2 (Topically) from sixth to twenty first day.

Tabular Column:

S.no	Grouping	Treatment
1	I	Normal control
2	II	Treated with Ultraviolet radiation at 365nm for 30 mins into a dorsal surface of skin for five days.
3	III	Treated with Ultraviolet radiation at 365nm for 30mins into a dorsal surface of skin for five days then treated with Tretinoin gel 0.04%w/w (positive standard) 12.5mg/cm^2 (Topically) from sixth to twenty first day.
4	IV	Treated with Ultraviolet radiation at 365nm for 30 mins into a dorsal surface of skin for five days. Then treated with

		Zingiber officinale roscae gel 1% (low dose of test drug) 12.5mg/cm^2 (Topically) from sixth to twenty first day.
5	V	Treated with Ultraviolet radiation at 365nm for 30mins into a dorsal surface of skin for five days then treated with *Zingiber officinale roscae* gel 5% (high dose of test drug) 12.5mg/cm^2 (Topically) from sixth to twenty first day

PARAMETERS:

- Macroscopic Examination
- Histopathological analysis

Macroscopic Examination:

Macroscopic Examination on Group I, II, III, IV, V evaluated by Severity Index (Severity score) of Psoriatic lesions on 9^{th,} 13th, 17th, 21st day was recorded.

0 = Clear skin

1 = Scaling of skin

2 = Scaling and redness of skin

3 = Scaling, redness and erythema in skin

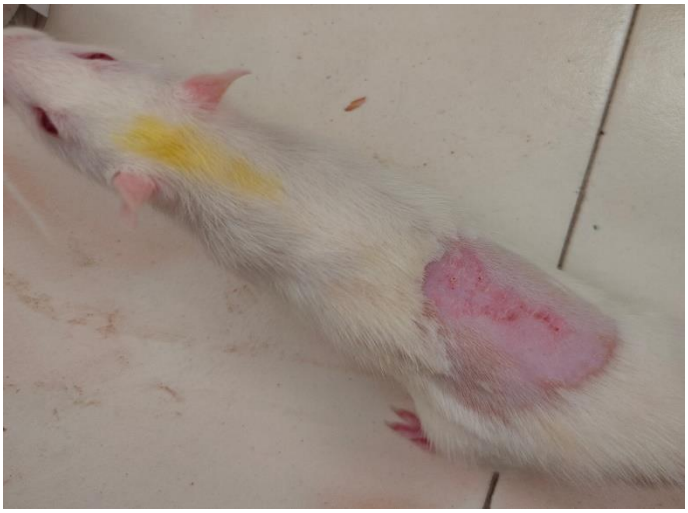


Fig no 8: Severity of psoriasis

Histopathological analysis:

On 21st day Group I, II, III, IV, V was anaesthetized and sacrificed. Dorsal part of skin from Group I, II, III, IV V was collected and preserved in glass container containing 21% formalin solution. Longitudinal sections of skin specimens (about 5 mm thickness) prepared by microtome and stained with Hematoxylin-eosin dye for Histopathological examination. The thickness of the cellular part of epidermis is determined using a calibrated ocular micrometer and all measurements are adjusted for magnification optics. (44)

0- No changes.

1-Slightly Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin.

2-Low to moderate Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin

3-Pronounced Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin

4-Excess Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin

7.2.2 IMIQUIMOD CREAM 5% w/w INDUCED PSORIASIS IN WISTAR RATS

Chemicals:

Inducing agent: Imiquimod cream 5% w/w

Experimental procedure:

The Wistar rat was divided into five groups of six each. Group I treated as normal control. Group II treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 (Topically) at ear surface for 21 days. The Group III treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 at ear surface for 21 days. Followed by Clobetasol propionate cream 0.02%w/w (Positive standard) 0.314mg/cm^2 (Topically) for 21 days. Group IV treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 at ear surface for 21 days. Followed by *Zingiber officinale roscae* gel 1% (low dose of test drug) 0.314mg/cm^2. (Topically) Group V treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 Followed by *Zingiber officinale roscae* gel 5%(high dose of test drug.) 0.314mg/cm^2 (Topically) [45]

Tabular column:

Grouping	**Treatment**
I	Normal control
II	Treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 (Topically) at ear surface for 21 days.
III	Treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 at ear surface for 21 days. Followed by Clobetasol propionate cream 0.02%w/w (Positive standard) 0.314mg/cm^2 (Topically) for 21 days.
IV	Treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 at ear surface for 21 days. Followed by *Zingiber officinale roscae* gel 1% (low dose of test drug) 0.314mg/cm^2(Topically).
V	Treated with Imiquimod cream 5%w/w (Negative control) 0.314mg/cm^2 Followed by *Zingiber officinale roscae* gel 5% (high dose of test drug.) 0.314mg/cm^2(Topically)

PARAMETERS:

- Body weight
- Histopathological Examination

Body weight:

On 1 st and 21 st day Body weight for Group I, II, III, IV, V was measured.

Histopathological analysis:

On 21st day Group I, II, III, IV, V were anaesthetized and sacrificed. Ear region from Group I, II, III, IV, V was collected and preserved in glass containers containing 21% formalin solution. Longitudinal sections of Ear specimens (about 5 mm thickness) prepared by microtome and stained with Hematoxylin-eosin dye for Histopathological examination. The thickness of the cellular part of epidermis is determined using a calibrated ocular micrometer and all measurements are adjusted for magnification optics [(44)]

0- No changes.

1-Slightly epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region

2-Low to moderate epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region

3-Pronounced epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region

4-Excess epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region[(44)]

7.3 INVITRO ANTIPSORIATIC ACTIVITY:

Estimation of Interleukin-23 on UV-Radiation induced Psoriasis by Elisa:

On 21 st Group I, II, III, IV, V was anesthetized and sacrificed and Skin punches measuring 6mm will be homogenized in 1.5mL extraction buffer (containing 10mM Tris ph. 7.4 150mM Nacl1% triton X-100) per gram of tissue using a glass homogenizer. The homogenates will be transferred to 1.5 mL eppendorf tubes, centrifuged at 13,000g for 10 minutes at 4˚c and the supernatant were used to determine Interleukin-23[45]

8.STATISTICAL ANALYSIS

Data were analyzed using One-way ANOVA (Dunnett's comparison test) and Two-way ANOVA(Tukey's comparison test) expressed as Mean± Standard Error of Mean (SEM). Statistical analyses were performed using Graph Pad Prism version 9.3, for windows. Differences between mean values of different groups were considered statistically significant at ($P<0.0001$)**** ($P<0.001$)***, ($P<0.01$)**, ($P<0.05$)*, ns- non significant.

RESULTS

9. RESULT:

9.1 PHYTOCHEMICAL ANALYSIS

Table 1:

S.NO	PHYTOCONSTITUENTS	OBSERVATION
1.	Tannins	+
2.	Flavanoids	+
3.	Phenol	+
4.	Saponin	+
5.	Ascorbic acid	+
6.	Reducing sugar	+
7.	Resin	+
8.	Balsams	+
9.	Chalcone	+
10.	Glycoside	+
11.	Volatile oil	+
12.	Aminoacid	+
13.	Phlobotannins	+
14.	Anthraquinones	+
15.	Steroids	+
16.	Gums	-

(+) Indicates the presence of chemical constituents

(-) Indicates the absence of chemical constituents

9.2 Effect of ZOR Gel in Scoring index on UV-Radiation induced Psoriasis in Wistar rats

Table 2:

PSORIASIS SCORE				
GROUPS	**9TH DAY**	**13 TH DAY**	**17 TH DAY**	**21 ST DAY**
Group I	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Group II	7.67±0.21 a^{****}	7.67±0.21 a^{****}	7.67±0.21. a^{****}	7.67±0.21 a^{****}
Group III	6.67±0.21 $a^{****}b^{****}$	5.83±0.41 a^{****} b^{****}	4.83±0.17 $a^{****}b^{****}$	2.00±0.26 $a^{****}b^{****}$
Group IV	7.00±0.26 a^{****} b^{ns} c^{ns}	6.50±0.22 $a^{****}b^{*}c^{ns}$	6.33±0.17 $a^{****}b^{**}c^{**}$	5.67±0.21 $a^{****}b^{****}c^{**}$
Group V	6.50±0.22 $a^{****}b^{*}c^{ns}$	5.83±0.17 $a^{****}b^{****}c^{ns}$	4.67±0.21 $a^{****}b^{****}$ c^{ns}	1.83±0.31 $a^{****}b^{****}c^{ns}$

The values are represented in Mean ± SEM, n=6

The Statistical significance test for comparison was done by Two-way ANOVA followed by Tukey's multiple comparison test where ****is ($p<0.0001$), ***is ($p<0.001$), **($p<0.01$), * is ($p<0.05$), ns is non-significant.

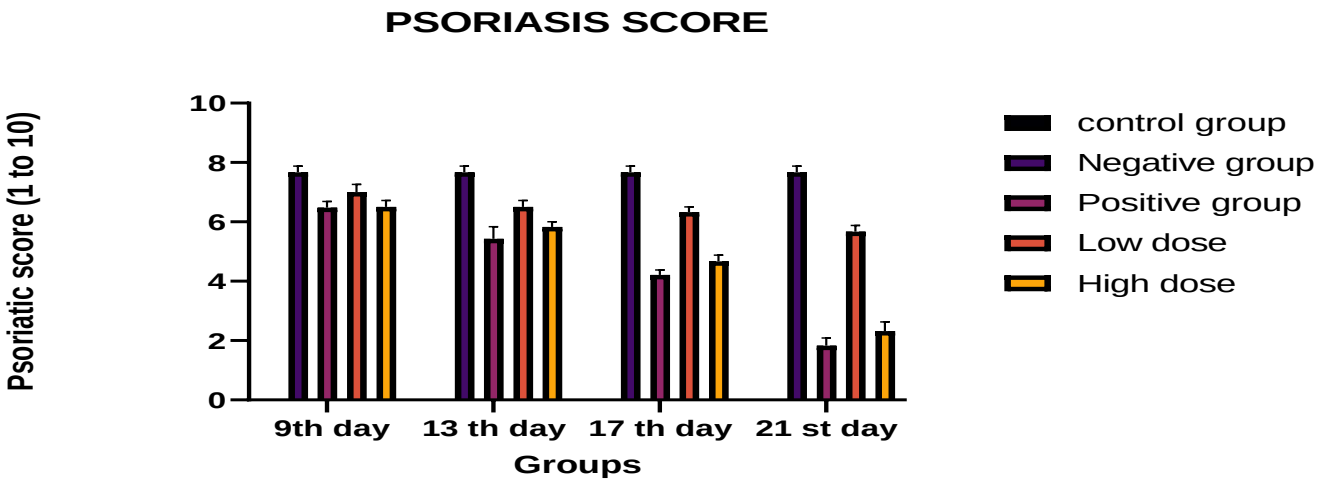


Figure 9: Effect of ZOR Gel in Scoring index on UV-Radiation induced Psoriasis in Wistar rats

9.3 Effect of ZOR Gel in Bodyweight on Imiquimod Cream 5% w/w induced Psoriasis in Wistar rats

Table 3:

BODY WEIGHT				
GROUPS	**1ST DAY**	**7TH DAY**	**14 TH DAY**	**21 ST DAY**
GROUP	147.50±0.76	147.50±0.76	147.50±0.76	147.50±0.76
GROUP II	145.33±0.80 a^{ns}	140.50±0.76 a^{****}	140.50±0.76 a^{****}	140.50±0.76 a^{ns}
GROUPIII	146.33±0.67 $a^{ns}b^{ns}$	127.83±2.18 $a^{****}b^{****}$	132.33±1.91 $a^{****}b^{**}$	140.83±0.75 $a^{*}b^{ns}$
GROUP IV	146.67±0.80 $a^{ns}b^{ns}c^{ns}$	127.00±1.88 $a^{****}b^{****}c^{ns}$	130.83±0.75 a^{****} $b^{*}c^{ns}$	137.67±0.42 $a^{****}b^{ns}c^{ns}$
GROUP V	146.50±0.76 $a^{ns}b^{ns}c^{ns}$	126.00±2.07 $a^{****}b^{****}c^{ns}$	130.50±2.25 $a^{****}b^{****}c^{ns}$	143.17±0.70 $a^{ns}b^{ns}c^{ns}$

The values are represented in Mean±SEM, n=6

The Statistical significance test for comparison was done by Two-way ANOVA followed by Tukey's multiple comparison test where ****is ($p<0.0001$), ***is ($p<0.001$), **($p<0.01$), * is ($p<0.05$), ns is non-significant.

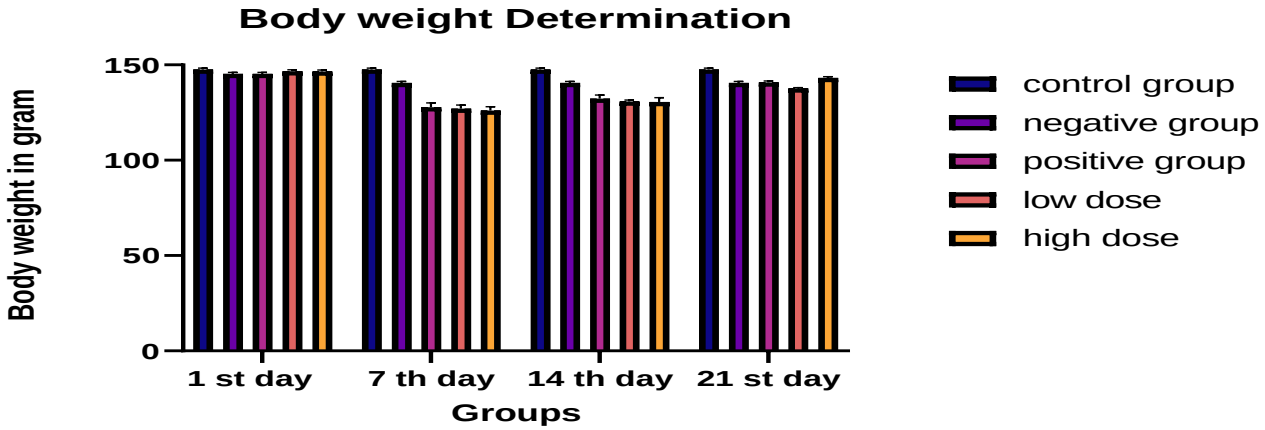


Figure 10: Effect of ZOR Gel in Bodyweight on Imiquimod Cream 5% w/w induced Psoriasis in Wistar rats

9.4 Estimation of Interleukin-23 on UV-Radiation Induced Psoriasis in Wistar rats

Table 4:

GROUPING	**INTERLEUKIN-23 (pg/ml)**
GROUP I: CONTROL	31.22±0.57
GROUP II: NEGATIVE CONTROL	61.83±1.90 a^{****}
GROUP III: POSITIVE CONTROL	31.05±0.92 a^{ns} b^{****}
GROUP IV:(LOW DOSE)	33.05±0.46 $a^{***}b^{****}c^{**}$
GROUP V:(HIGH DOSE)	30.40±0.56 $a^{ns}b^{****}c^{ns}$

The values are represented in Mean±SEM, n=6

The Statistical significance test for comparison was done by One-way ANOVA followed by Dunnett's multiple comparison test where ****is ($p<0.0001$), ***is ($p<0.001$), **($p<0.01$), * is ($p<0.05$), ns is non-significant.

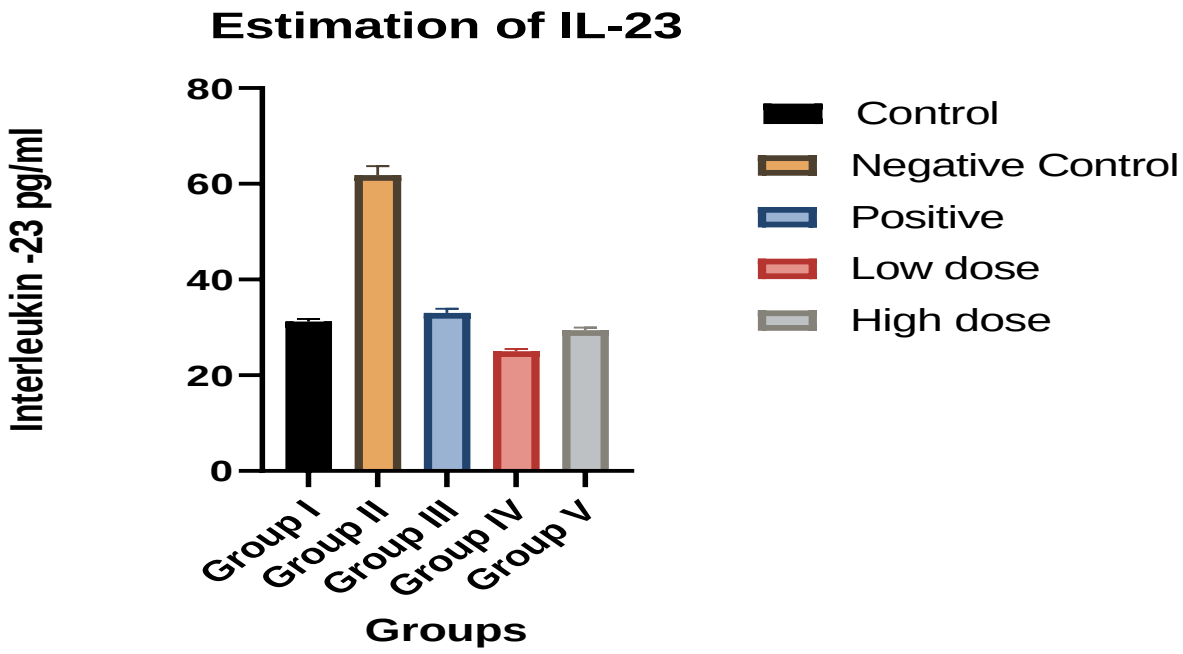
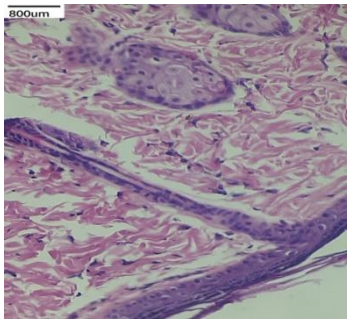


Figure11: Estimation of Interleukin-23 on UV-Radiation Induced Psoriasis in Wistar rats

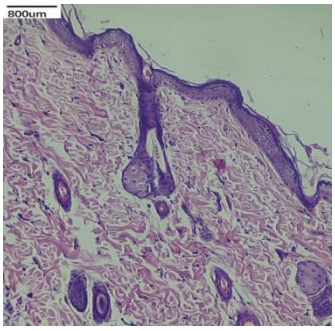
9.5 Histopathological Examination of Ear on Imiquimod cream 5% w/w induced Psoriasis in Wistar Rats.

Figure 12:

Group I



Group II



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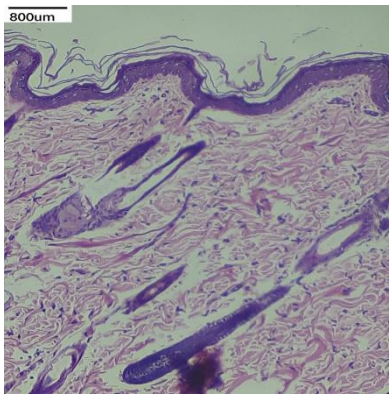

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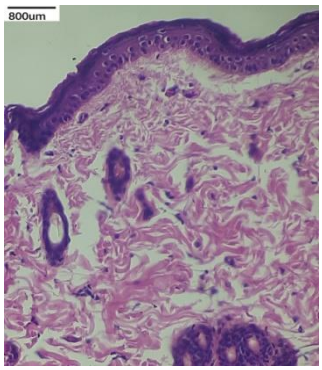
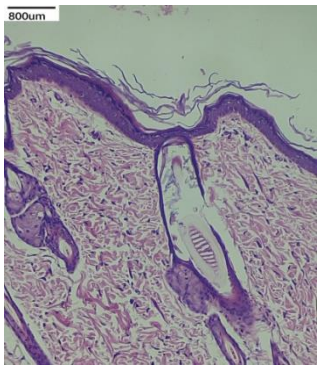


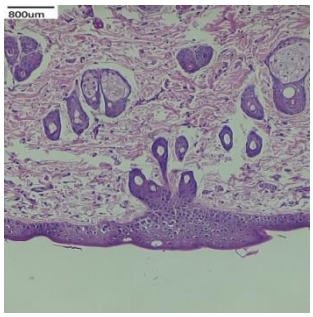
Group V



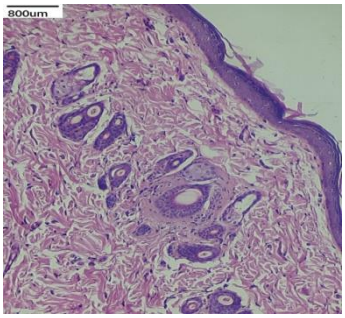
9.6 Histopathological Examination of Skin on UV-Radiation induced Psoriasis in Wistar Rats

Figure 13:

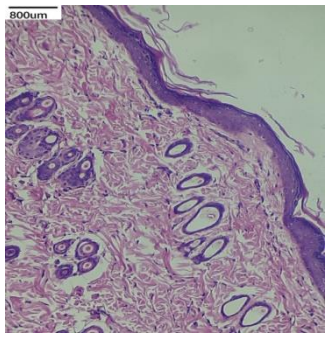
Group I



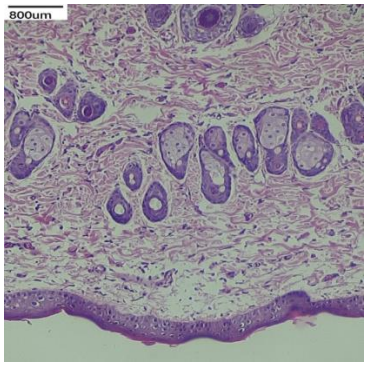
Group II



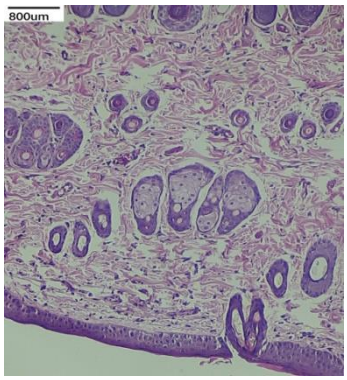
Group III



Group IV



Group V



OBSERVATIONS

10. OBSERVATION

10.1PHYTOCHEMICAL ANALYSIS:

The Results of Preliminary Phytochemical screening of Ethanolic extract of *Zingiber officinale roscae s*howed the presence of Tannins, Flavanoids, Phenol, Saponin, Ascorbic acid, Reducing sugar Resins, Balsams, Chalcone, Glycosides, Volatile oil, Aminoacid, Phlobotannins, Sterioids and absence of gums and mucilage

10.2 INVIVO ANTI-PSORIATIC STUDY RESULTS:

10.2 Effect of ZOR Gel in Scoring index on UV-Radiation induced Psoriasis in Wistar rats

9th Day:

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II, III, IV, V Psoriatic score was significantly ($p<0.0001$) increased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Psoriatic score was significantly ($p<0.0001$) decreased.

When Group II was compared to Group IV Psoriatic score was non significantly (ns) decreased.

When Group II was compared to Group V Psoriatic score was significantly ($p<0.05$) decreased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Psoriatic score was non significantly ($p<0.0001$) increased.

When Group III was compared to Group V Psoriatic score was non significantly ($p<0.0001$) decreased.

13th Day:

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II, III, IV, V Psoriatic score was significantly ($p<0.0001$) increased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Psoriatic score was significantly ($p<0.0001$) decreased.

When Group II was compared to Group IV Psoriatic score was significantly ($p<0.05$) decreased.

When Group II was compared to Group V Psoriatic score was significantly ($p<0.0001$) decreased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Psoriatic score was non significantly (ns) increased.

When Group III was compared to Group V Psoriatic score was non significantly (ns) decreased.

17^{th} Day:

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II, III, IV, V Psoriatic score was significantly ($p<0.0001$) increased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Psoriatic score was significantly ($p<0.0001$) decreased.

When Group II was compared to Group IV Psoriatic score was significantly ($p<0.01$) decreased.

When Group II was compared to Group V Psoriatic score was significantly ($p<0.0001$) decreased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Psoriatic score was significantly ($p<0.01$) increased.

When Group III was compared to Group V Psoriatic score was non significantly (ns) increased.

21st Day:

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II, III, IV, V Psoriatic score was significantly ($p<0.0001$) increased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Psoriatic score was significantly ($p<0.0001$) decreased.

When Group II was compared to Group IV Psoriatic score was significantly ($p<0.0001$) decreased.

When Group II was compared to Group V Psoriatic score was significantly ($p<0.0001$) decreased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Psoriatic score was significantly ($p<0.01$) increased.

When Group III was compared to Group V Psoriatic score was non significantly (ns) decreased.

10.3 Effect of ZOR Gel in Bodyweight on Imiquimod Cream 5% w/w induced Psoriasis in Wistar rats

1st Day

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II, III, IV, V Body weight was non significantly(ns) decreased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Body weight was non significantly (ns) increased.

When Group II was compared to Group IV Body weight was non significantly (ns) increased.

When Group II was compared to Group IV Body weight was non significantly (ns) increased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Body weight was non significantly (ns) increased.

When Group III was compared to Group IV Body weight was non significantly (ns) increased.

7th Day

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II, III, IV, V Body weight was significantly ($p<0.0001$) decreased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Body weight was significantly ($p<0.0001$) decreased.

When Group II was compared to Group IV Body weight was significantly ($p<0.0001$) decreased.

When Group II was compared to Group IV Body weight was significantly ($p<0.0001$) decreased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Body weight was non significantly (ns) decreased.

When Group III was compared to Group IV Body weight was non significantly (ns) decreased.

14th Day

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II, III, IV, V Body weight was significantly ($p<0.0001$) decreased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Body weight was significantly ($p<0.01$) decreased.

When Group II was compared to Group IV Body weight was significantly ($p<0.05$) decreased.

When Group II was compared to Group V Body weight was significantly ($p<0.0001$) decreased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Body weight was non significantly (ns) decreased.

When Group III was compared to Group IV Body weight was non significantly (ns) decreased.

21th Day

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II Body weight was non significantly (ns) decreased.

When Group I was compared to Group III Body weight was significantly ($p<0.05$) decreased.

When Group I was compared to Group IV Body weight was significantly ($p<0.0001$) decreased.

When Group I was compared to Group V Body weight was non significantly (ns) decreased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Body weight was non significantly(ns) increased.

When Group II was compared to Group IV Body weight was non significantly(ns) decreased.

When Group II was compared to Group IV Body weight was non significantly(ns) increased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Body weight was non significantly (ns) decreased.

When Group III was compared to Group V Body weight was non significantly (ns) increased.

10.4 Estimation of Interleukin-23 on UV-Radiation Induced Psoriasis in Wistar rats

Group I was compared with Group II, III, IV, V is considered as 'a'

When Group I was compared to Group II Interleukin-23 was significantly ($p<0.0001$) increased.

When Group I was compared to Group III Interleukin-23 was non significantly (ns) decreased.

When Group I was compared to Group IV Interleukin-23 was significantly ($p<0.001$) Increased.

When Group I was compared to Group V Interleukin-23 was non significantly (ns) decreased.

Group II was compared with Group III, IV, V is considered as 'b'

When Group II was compared to Group III Interleukin-23 was significantly ($p<0.0001$) decreased.

When Group II was compared to Group IV Interleukin-23 was significantly ($p<0.0001$) decreased.

When Group II was compared to Group V Interleukin-23 was significantly (0.0001) decreased.

Group III was compared with Group IV, V is considered as 'c'

When Group III was compared to Group IV Interleukin-23 was significantly ($p<0.01$) increased.

When Group III was compared to Group V Interleukin-23 was non significantly (ns) decreased.

10.5 Histopathological Examination of Ear on Imiquimod cream 5% w/w induced Psoriasis in Wistar Rats.

Group I

The Histopathological examination of the ear shows no changes (Figure 12)

Group II

The Histopathological examination of ear shows Severe epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region (Figure 12)

Group III

The Histopathological examination of ear shows moderate epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region (Figure 12)

Group IV

The Histopathological examination of ear show pronounced epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region (Figure 12)

Group V

The Histopathological examination of ear shows low epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis in ear region (Figure 12)

10.6 Histopathological Examination of Skin on UV-Radiation induced Psoriasis in Wistar Rats

Group I

The Histopathological examination of skin epidermis shows no changes (Figure13)

Group II

The Histopathological examination of skin epidermis shows Severe Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin. (Figure13)

Group III

The Histopathological examination of skin epidermis shows moderate Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin (Figure13)

Group IV

The Histopathological examination of skin epidermis shows Pronounced Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin (Figure13)

Group V

The Histopathological examination of skin epidermis shows low Hyperkeratosis, parakeratosis, and acanthosis in epidermis of skin (Figure13)

DISCUSSION

11. DISCUSSION

Psoriasis is a chronic, non-communicable, painful, disfiguring and disabling disease for which there is no cure and with great negative impact on patients' quality of life (QoL). It can occur at any age, and is most common in the age group 50–69. The reported prevalence of Psoriasis in countries ranges between 0.09% and 11.4%, making Psoriasis a serious global problem. The Etiology of Psoriasis remains unclear, although there is evidence for genetic predisposition. The role of the immune system in Psoriasis causation is also a major topic of research. (1)

Psoriasis occurs worldwide. It affects men and women of all ages, regardless of ethnic origin, in all countries. Data on the prevalence of psoriasis in countries vary between 0.09% and 11.4%. In most developed countries, prevalence is between 1.5 and 5%. There is also evidence to suggest that the prevalence of psoriasis may be increasing. (11)

The pathophysiology of Psoriasis is not completely understood. It involves multiple factors, including genetic, immunologic, environmental, stress factors contributing to the development of disease. Cytokines are locally acting protein mediators that are involved in almost all the biological processes including cell growth, activation, inflammation, immunity, and differentiation. Activated T cells are the primary modulators in the pathogenesis of Psoriasis. Disordered cellular immunity involving inflammatory cytokines IL-1 (interleukin-1), IL-6, TNF-α (Tumour necrosis factor) and pro-inflammatory transcription factor has been implicated.

T cells are differentiated into four types Th1 (T helper cell), Th2, Th17, T regulatory cells.) these activated cells enter the circulation and extravasate through the endothelium to the sites of inflammation in skin where they produce Th1, Th2, and Th17 imbalance. The role of IL-23, Th -17 pathway has been researched in recent years IL-23 is a heterodimer produced by dentric cells and macrophages it causes activation of Th -17 cells to produce IL-17, IL-22, (psoriatic skin contain high level of IL-23 compared to normal skin.IL-17 is critical for pathogenesis of Psoriasis. Elevated levels of IL-17 result in increase in level of pro-inflammatory cytokines like S-210, A7, β-defences and lipocalin. In addition, increased level of IL-17 also promotes keratinocytes to produce CXC-chemokine's and ccl-20 both of which attract neutrophils to the site of inflammation. Increased IL-22 levels lead to epidermal acanthosis and keratinocyte differentiation. (21)

The Management of Psoriasis is a Multidisciplinary approach in order to reduce the Scaling, Redness, Erythema. So the Beneficial effects are probably related to inhibition of Interleukin-

23 production.

Herbal plants provide most of the medicinal needs. Important herbal products include spices, herbal teas, functional foods, medicinal raw materials, essential oils, flavouring and dietary supplements.The medicinal use of plant is as a result of the phyto-constituents present in them. *Zingiber officinale roscae* gel provide most of the medicinal needs. Some of these chemicals is bioactive and produce definite physiological and biochemical actions. *Zingiber officinale roscae* gel is widely used in Indian cookery from centuries and have a versatile role to play in traditional medicine. Its medicinal uses are Anti-platelet activity, Cancer, Inflammation, and Powerful antioxidant. [(24)]

Ultraviolet Radiation at 365nm is used to induce Psoriasis in rat. Rat skin responded to Ultraviolet radiation is quite different from human, guinea-pig, or mouse skin. Rat was characterized by a sharply demarcated brownish-red lesion with scale formation lasting for 21 days. Histopathologically, Microvascular dilatation, Intraepidermal accumulation of polymorphonuclear leucocytes with microabscess, mononuclear cell infiltration at the papillary dermis and hyperproliferation of epidermal cells occurs. These features were similar to those of clinical psoriasis vulgaris in man. T cells are differentiated into four types Th1 (T helper cell), Th2, Th17, T regulatory cells. These activated cells enter the circulation and extravasate through the endothelium to the sites of inflammation in skin where they produce Th1, Th2, and Th17 imbalance. [(20)]

Imiquimod Cream 5%w/w application on mouse ear for 21 days induced inflamed scaly lesions resembling plaque type psoriasis. These lesions showed increased epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis, and infiltrates consisting of $CD4^+$ T cells, $CD11c^+$ dendritic cells, and plasmacytoid dendritic cells. IMQ induced epidermal expression of IL-23, IL-17A, and IL-17F, as well as an increase in splenic Th17 cells. IMQ-induced Psoriasis was partially dependent on the presence of T cells, whereas disease development was almost completely blocked-in mice deficient for IL-23 or the IL-17 receptor, demonstrating a pivotal role of the IL-23/IL-17 axis. In conclusion, the sole application of the IMQ rapidly induce Psoriasis closely resembling human psoriasis, critically dependent on the IL-23/IL-17 axis. [(21)]

Tretinoin is the first line drug for most patients with Psoriasis. The efficacy of Tretinoin in the treatment of Psoriasis was first demonstrated by Kligman using an animal model of Psoriasis. Application of Tretinoin also blocked UV-induced activation of the nuclear transcription factors AP-1 and NF-κB. The most common and frequent adverse effect of topical retinoids are known as ‘retinoid reaction’, characterized by pruritus, burning sensation

at the sites of application, erythema, peeling. [14]

Clobetasol propionate is the most potent of all topical steroids. It is successfully applied in the treatment of various skin diseases such as psoriasis and vulvar lichen sclerosus. The therapy is, however, mainly symptomatic. Clobetasol propionate exerts antiinflammatory, immunosuppressive and antimitotic effects influencing the growth, differentiation and function of various cells and inhibiting cytokine production. Seven different dosage forms are available to deliver the drug to the living cells of the skin. The potency of clobetasol propionate, however, is accompanied by local and systemic side effects, such as skin atrophy and hypothalamic-pituitary-adrenal axis suppression. [14]

Some of the other treatments are amcinonide 0.1%, betamethasone dipropionate, betamethasone valerate as 0.1%, 0.12% and 1%, halcinonide 0.1%, desoximetasone 0.25% and mometasone furoate other examples are Anthralin, Coal tar, Retinoid, Methotrexate, Cyclosporine, phototherapy. [14]

Severity Index (Severity score) is used to assess the grade and severity of scoring lesions, scaling, redness and erythema of Psoriasis

Histopathological Examination of dorsal skin describes about the Hyperkeratosis, Parakeratosis, and Acanthosis of the epidermis of Psoriasis.

Interleukin-23 is a key cytokine for promoting inflammatory responses in a target organs in Psoriasis

Body weight is used to assess the progression of the disease like Psoriasis

Decrease in body weight occurs in many chronic diseases, such as diabetes, cancer, as well as in inflammatory diseases such as Crohn's disease, sepsis and Psoriasis.

Histopathological Examination is used to examine the ear sample and describes about the epidermal proliferation, abnormal differentiation, epidermal accumulation of neutrophils in microabcesses, neoangiogenesis.

UV-Radiation induced Psoriasis in Wistar Rats

Severity Index (Severity score) is used to assess the grade and severity of scoring lesions, scaling, redness and erythema of Psoriasis.[44]

In this study, the Scoring Index of Psoriasis in UV-Radiation induced Psoriasis for Low dose and High dose of ZOR (1% and 5% respectively) gel and Tretinoin gel (0.04%w/w) treated reduced the Lesions, scaling, redness of Psoriasis elicits Anti-psoriatic effect of ZOR gel.

Hyperkeratosis, Parakeratosis, and Acanthosis of the epidermis are the Histopathological symptoms of Psoriasis.[44]

In this study, the Histopathological results showed that UV-Radiation induced Psoriasis treated with Low and High dose of ZOR (1% and 5% respectively) gel and Tretinoin gel 0.04%w/w reduced Hyperkeratosis, Parakeratosis, and acanthosis in epidermis of skin elicits Anti-Psoriatic effect of ZOR gel.

Interleukin-23 is a key cytokine for promoting inflammatory responses in a target organs in Psoriasis. [44]

In this study, Interleukin-23 in UV-Radiation induced Psoriasis for low and high dose of ZOR (1% and 5% respectively) gel and Tretinoin gel 0.04%w/w reduced the level of Interleukin-23 elicits Anti-Psoriatic effect of ZOR gel.

Imiquimod 5%w/w cream induced Psoriasis in Wistar rats

Body weight is used to assess the progression of the disease like Psoriasis

Decrease in body weight occurs in many chronic diseases, such as diabetes, cancer, as well as in inflammatory diseases such as Crohn's disease, sepsis and Psoriasis.[45]

Body weight Measured in Imiquimod cream 5% w/w induced Psoriasis for Low and High dose of ZOR(1% and 5% respectively) gel and Clobetasol propionate Cream 0.05%w/w increased body weight elicits Anti-Psoriatic effect of ZOR gel.

Epidermal proliferation, Abnormal differentiation, Epidermal accumulation of neutrophils in microabcesses, neoangiogenesis of the ear are the symptoms of Psoriasis[45]

The Histopathological Results Showed Imiquimod cream 5%w/w induced Psoriasis of Low and High dose of ZOR(1% and 5%respectively) gel and Clobetasol propionate Cream 0.05%w/w reduced Epidermal proliferation, Abnormal differentiation, Epidermal accumulation of neutrophils in microabcesses, Neoangiogenesis of ear elicits Anti-Psoriatic

CONCLUSION

12. CONCLUSION

It may be Concluded that Ethanolic extract of ZOR gel showed Reduction of the Scoring Index (Severity score) such as Scaling, Lesions, Redness, Erythema and decrease in Interleukin-23 in the skin of UV-Radiation induced Psoriasis model.

Histopathological study of the skin showed Normal architecture with reduction in Hyperkeratosis, Parakeratosis, and Acanthosis.

Increase in Body weight of Imiquimod cream 5%w/w induced Psoriasis model

Histopathological study of the Ear showed Normal architecture with reduction in Epidermal proliferation, Abnormal differentiation, Epidermal accumulation of neutrophils in microabcesses, Neoangiogenesis.

Clobetasol propionate cream 0.05%w/w and Tretinoin gel 0.04%w/w act by inhibiting the synthesis of Inflammatory mediator Interleukin-23. ZOR gel also act by inhibiting the synthesis of Inflammatory mediator Interleukin-23 thus, it may be concluded that ZOR gel has significant Anti-Psoriatic activity.

Anti-psoriatic activity was found significant in *Zingiber officinale roscae* may be due to the presence of Vitamin A Beta-Carotene. Further studies to isolate the Chemical constituents responsible for the Anti-Psoriatic activity is required.

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