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Metadichol, A Novel ROR Gamma Inverse Agonist and Its Applications in Psoriasis

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Abstract

Psoriasis affects 3% of the population worldwide, and there is no known cure. Psoriasis is associated with an increased risk of psoriatic arthritis, lymphomas, cardiovascular disease, and Crohn's disease. Psoriasis treatments today include steroid and vitamin D3 cream, ultraviolet light, and immune systemsuppressing medications such as methotrexate.

The T cells responsible for psoriasis are Th1 and Th l7 cells. IL-22, produced by Th17 cells, is crucial for the proliferation of keratinocytes. IL-22 with the help of IL-17 can induce the critical events of psoriasis. To maintain Th17 cells, IL-23 is required, and it is released from tumor necrosis factor-alpha (TNF-alpha) induced pathways. The pathophysiology of psoriasis involves RORC (retinoic acid receptor-related orphan nuclear receptor gamma) as a critical transcription factor for the development of Th17 cells. FDA has approved an antibody Secukinumab® targeting TNF-α for the treatment of psoriasis. Other FDA approved drugs are Tremfya® targeting IL23 for treatment of moderate to severe plaque psoriasis and Taltz® that blocks IL17 for treatment of plaque psoriasis.

Metadichol® a nanoformulation of long-chain lipid alcohols derived from food is a TNF-alpha inhibitor and also binds to Vitamin D receptor (VDR) that could have beneficial effects on Psoriasis. VDR modulates Th1-mediated inflammatory disease like psoriasis. We now present evidence that Metadichol is an inverse agonist of RORγt and AHR (Aryl Hydrocarbon Receptor) thus controlling Th17, IL17 and IL22. Being a TNF-alpha inhibitor, it can control IL23 thus blocking the significant pathways that exacerbate psoriasis. We present case studies of 7 patients afflicted with psoriasis and skin related conditions and how treatment with Metadichol resolved the underlying disease. Metadichol® has properties that allow its use as a safe nontoxic, toxic solution to combating the growing number of psoriasis cases.

Keywords: Metadichol; psoriasis; Nuclear receptors; Atopic dermatitis; VDR; AHR; TNF alpha; ICAM1; Vitamin D; Calcitriol; Inverse agonist; RORC; Retinoic acid-related nuclear receptor gamma; IL17; IL22; IL23; Th17; Th1; TH2; Long chain alcohols

Introduction

RORC (Retinoic acid-related nuclear receptor gamma) is a nuclear receptor that is expressed in the immune system cells and is an essential transcription factor in cell differentiation [1]. RORC may be useful in preventing, and treatment of immune-mediated inflammatory diseases which leads to many autoimmune diseases like including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease and psoriasis [2,3].

T helper (TH) cells are an essential part of the immune system because they coordinate defense against pathogens, and their cytokines and effector functions mediate different types of tissue inflammation [4]. TH17 cells, one of the subsets of effector T helper cells, play a critical role in host defense against pathogens and are potent inducers of autoimmunity and tissue inflammation. Th17 cells are a subset of CD4+ T cells. They produce the cytokines IL17A, IL17F, IL-21, and IL-22 that stimulate tissue cells to promote recruitment of granulocytes and produce inflammatory chemokines, cytokines, and metalloproteases. Elevated levels of IL17, the central cytokine produced by Th17 cells, are expressed in several allergic and autoimmune diseases. Studies have shown that RORγ deficient mice are healthy and less susceptible to disease conditions [5].

IL-23 is a cytokine which is required for Thl7 cell survival. IL-23 deficient mice do not produce Thl7 cells and are resistant to diseases like inflammatory bowel disease (IBD). Research reveals a connection between the polymorphisms of the genes for Th17 cell-surface receptors, IL-23R, and CCR6 and susceptibility to IBD, multiple sclerosis (MS), rheumatoid arthritis (RA), and psoriasis [6]. Recent work has that Vitamin D down regulates the IL-23 receptor pathway [7].

The anti-p40 monoclonal antibody Ustekinumab (Stelara) that blocks IL-12 and IL-23 have been approved for treatment for moderate to severe plaque psoriasis in adult patients [8]. Clinical studies on monoclonal antibodies that target IL-23 and inhibit the Th17 subset selectively are currently underway for the treatment of psoriasis. Recent phase II clinical results using both anti-IL-1 and anti-IL-17 therapeutic antibodies demonstrated excellent efficacy in patients with chronic psoriasis [9].

The accumulated data point out to the importance of inhibition of the Th17 pathway as a viable clinical target for the treatment of immune-mediated inflammatory diseases. Inhibition of Th17 through the use of compounds with ROR gamma modulation activities is a promising and potentially beneficial approach that may provide useful treatment of these immune diseases [10]. Three ROR gamma antagonists (inverse agonists) are in clinical development [11]. RORγ role in Th17 cell differentiation, and the increasing clinical validation for IL-17 and other Th17 derived cytokines in autoimmune diseases,

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makes RORC a compelling target. Neutralizing IL-17 with antibodies has proved ineffective in patients with inflammatory bowel disease. TH17 cells express IL-17 together with IL-17F, IL-22, IL-26, and granulocyte-macrophage-colony-stimulating factor. Inhibition of Th17 cell lineage is a highly preferred route to blocking a single effector cytokine. Targeting interleukin-17 (IL-17) produced by T helper cells has been validated clinically to treating psoriasis, psoriatic arthritis, and ankylosing spondylitis. FDA has approved antibody Secukinumab from Novartis targeting TNF-α and interleukin-12/23. [12].

TNF-a is implicated in the pathogenesis of multiple inflammatory and autoimmune conditions such as like Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, and psoriasis. The development of TNF-α inhibitors has improved therapeutic options for patients with these conditions. However, TNF-α inhibitors are paradoxically inducing the new onset of psoriasis or worsening pre-existing quiescent psoriatic diseases [13].

Genomic effects of 1, 25(OH)2D3 are controlled *via* binding to a nuclear receptor protein, VDR (vitamin D receptor). VDR is expressed in keratinocytes, fibroblasts, Langerhans cells, sebaceous gland cells, endothelial cells and almost the entire cell types related to the skin immune system [14]. Vitamin D and analogs display in the skin effects on cellular differentiation, proliferation, regulate psoriasis and represent a standard therapy. However, there is a need for highly antiproliferative or anti-inflammatory acting vitamin D analogs that exhibit only minor calcemic activity. Selective vitamin D signaling pathways that exert little calcemic activity would lead to an effective dermatologic therapy in the topical or systemic treatment of various inflammatory skin diseases. The efficacy of topical treatment with vitamin D analogs in psoriasis can also be enhanced by combination with other therapies: tumor necrosis factor α (TNFα)-inhibitors [15-17].

Skin cells express the nuclear receptor, AHR (Aryl hydrocarbon receptor). AHR ligands are present in copious amounts in skin from exogenous or endogenous sources. AHR is a necessary factor for the production of IL-22 by Th17 [18]. Th17 cells are pivotal for fighting bacteria and uncontrolled lead to exacerbation of autoimmune diseases; thus, it is essential that they are tightly controlled. AHR activity promotes their expansion and is obligatory for IL-22 production. AHR also encourages IL21 and IL23 output and inhibitory effects on Th17 [19]. The skin has several subsets of IL-17 producing cells. IL-22 is controlled by AHR activity [20]. In humans, LC induces a particular subset of T cells, Th22, which produce IL-22 but not IL-17 [21]. IL-22 is under the control of AHR [22]. IL-22 participates in many chronic inflammatory conditions, including in the skin. AHR is a target for the treatment of psoriasis and is an essential player in skin physiology, and although much is still unclear. AHR emerges as a target for prevention and therapy of skin diseases the role of AHR in changing the balance of regulatory T cells [23] versus Th17 cells, AHR has been suggested as a target to combat autoimmune disorders [24].

Psoriasis affects 7.5 million Americans and an estimated 2–3% of the world's population [25]. While there have been several therapeutic advances in the last decade, 50% of patients with the disease are under-treated. And the rest report details dissatisfaction, for a myriad of reasons. Psoriasis is a complex, autoimmune disease ranging from mild to severe to life-threatening [26].

Given the fact Metadichol is a TNF alpha and ICAM-1 inhibitor, and it binds to VDR as an inverse agonist [27] and an inverse agonist of AHR [28]. We now show that it is also an inverse agonist of ROR gamma. Inhibition of-of IL-17 and TH17-cell activity in conjunction with inverse agonist activist against AHR and a TNF alpha inhibitor and the immune modulating properties mediated by VDR is an approach towards remission and prevention of chronic immune-mediated inflammatory diseases. Metadichol as we case show with multiple case studies seems to be capable of fulfilling that requirement in treating Psoriasis.

Experiment

Nuclear receptor (NR) assays

The assays were performed by Indigo Biosciences Inc, PA, USA using their proprietary assay methods.

Plasmids

This study utilized a hybrid receptor comprising the N-terminal Gal4 DNA binding domain fused to the ligand binding domain of the specific human nuclear receptor ROR Gamma). The reporter vectors used in these studies comprise the firefly luciferase gene functionally linked to either an upstream NR response element (NRE) or the Gal4 activation sequence (UAS).

Compound handling

Test compound was delivered as solution dissolved in water. Stock of test compounds was stored at room temperature as directed by the sponsor.

Set up of NR assays

The NR Assays were performed as depicted in Figures 1 and 2.

Step 1: A suspension of Reporter Cells was prepared in Cell Recovery Medium (CRM; containing 10% charcoal stripped FBS). For antagonist assays, reporter cells were supplemented with a 2x-EC80 concentration of the appropriate reference agonist. For agonist and antagonist assays, 100 ml of the Reporter Cell suspension was dispensed into the wells of white, cell culture treated, 96-well assay plates. For agonist and antagonist assays, 2x-concentration treatment media were prepared.

Step 2: Immediately prior to assay setup, test compounds were diluted using compound screening medium (CSM; containing 10% charcoal stripped FBS) to generate '2x-concentration' treatment media.

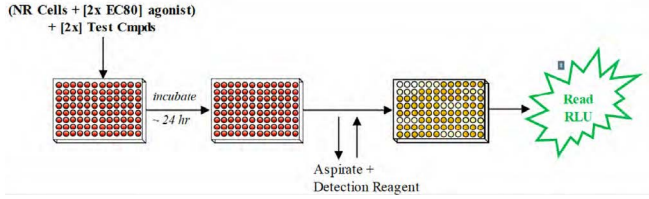

Figure 1: Agonist Assay.

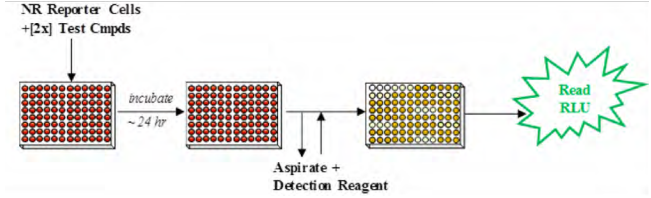

Figure 2: Antagonist Assay.

100 ml of each treatment medium was dispensed into triplicate assay wells pre-dispensed with Reporter Cells. Assay plates were incubated at 37°C for 24 h

Step 3: Following the 24 h incubation period, treatment media were discarded and 100 µl/well of Luciferase Detection Reagent was added. RLUs were quantified from each assay well to determine NR activity.

Assay validation

Reference compounds were utilized to confirm the performance of the specific lot of NR Reporter Cells treated with the Sponsor's test compounds. Reference Compound and Test Compound assays were performed at the same time and, hence, were exposed to the same assay reagents and environmental conditions. Refer to individual data sets for the identities of specific reference agonist and antagonist and their respective treatment concentration ranges. Reference groups always include a 'Vehicle' control to determine background activity in the assay and to calculate Fold Activation or Percent-Inhibition.

Data reduction

Microsoft Excel was used to manage and archive assay data, as well as to calculate average RLU values ± standard Deviation (SD), Fold-activation, Percent activation, Percent Coefficients of Variation (%CV), and Z' values.

Graphical data methods

Dose response curve (DRC) analyses of the reference compounds and test compounds were performed *via* non-linear curve-fitting of Fold-Activation *vs.* Log [Compound] for agonist assays. Percent Inhibition *vs.* Log [Compound] for antagonist and inverse agonist assays was performed using Graph Pad Prism software (Figure 3).

- **Percent Coefficient of Variation** (%CV) is:
  100*(SD/Ave. RLU)
- ***Fold*-Activation** in Agonist assays is:
  [Ave RLU $^{\text{Test Cmpd}}$ / Ave RLU $^{\text{Vehicle}}$]
- ***Percent*-Activation of Ref^{MAX}** is calculated by normalizing test cmpd RLU values to the maximum RLU value of the reference agonist (=100%), as follows:
  100*(Ave. RLU$^{\text{Test Cmpd}}$ / Ave RLU$^{\text{Reference Maximum}}$)
- **Z' for Reference *Agonists*** is:
  1-[(3*[SD$^{\text{Vehicle}}$ + SD$^{\text{Ref Cmpd}}$]) / (RLU$^{\text{Ref Cmpd}}$ - RLU$^{\text{Vehicle}}$)]
- ***Fold*-Inhibition in *Antagonist*** is:
  [Ave RLU $^{\text{EC80 agonist}}$ / Ave RLU $^{\text{Test Cmpd}}$]
- ***Percent*-Inhibition in *Antagonist***.
  The theoretical minimum inhibition (0% inhibition) derives from EC_{80} agonist treatment *only*, no treatment cmpd. % Inhibition is calculated as:
  100*(1-[Ave RLU $^{\text{Test Cmpd}}$ / Ave RLU $^{\text{EC80 agonist}}$)

Figure 3: Graphical Data Methods

Graphical data methods

Dose response curve (DRC) analyses of the reference compounds and test compounds were performed *via* non-linear curve-fitting of Fold-Activation *vs.* Log [Compound] for agonist assays. Percent Inhibition *vs.* Log [Compound] for antagonist and inverse agonist assays was performed using Graph Pad Prism software (Figure 3).

Assay results

Raw Data are shown in Figure 4. The results of the assay of standard Ursolic acid and of Metadichol are shown in Figures 5 and 6. Based on the EC50 values of the assay, Metadichol is a more powerful inverse agonist of ROR gamma than standard Ursolic acid.

Human Case Studies

Psoriasis case no. 1

Female 62, Psoriasis on legs for 44 years. She was sprayed with Metadichol in mouth and on the affected parts. Based on number of bottles used per month, the dosage was approximately 20 mg per day. During this time her arthritic pain associated with Psoriasis also decreased considerably. Patient is now normal and uses 5 mg of Metadichol orally every day (Figure 7).

Compound	Conc.	Human RORg Inverse Agonist Assays Host cell line: HEK							
		Luc1	Luc2	Luc3	AVG	SD	Fold-Inhibition	% Inhibition	% CV
Water	0.002	973,381	1,035,610	999,047	1,002,679	31,273	1.0	0.0	3.1
NRX-1119 (µg/ml)	0.0073	1,075,040	1,098,420	1,066,630	1,080,030	16,472	0.92838	-7.7	1.5
	0.024	1,143,280	1,136,480	1,040,420	1,106,727	57,524	0.90599	-10.37693	5.2
	0.081	1,059,630	1,146,330	1,270,690	1,158,883	106,089	0.86521	-15.57866	9.2
	0.27	1,046,700	994,534	1,018,520	1,019,918	26,111	1.0	-1.7	2.6
	0.90	732,807	642,883	683,129	686,273	45,044	1.5	31.556084	6.6
	3.0	133,972	113,328	123,758	123,686	10,322	8.1	87.664451	8.3
	10	1,454	958	1,540	1,317	314	761.094	99.86861	23.8
Reference Inverse Agonist: Ursolic acid (nM)	8.2	1031820	883264	978380	964,488	75,246	1.0	3.8	7.8	Z'
	24.691	1007870	883422	925596	938,963	63,292	1.1	6.4	6.7	
	74.074	801458	671315	745480	739,418	65,283	1.4	26.255819	8.8	
	222.22	471682	464306	456092	464,027	7,799	2.2	53.721329	1.7	
	666.67	155981	138640	135860	143,494	10,903	7.0	85.688977	7.6	0.9
	2000	21409.5	19784.4	24658.5	21,951	2,482	45.6785	97.810786	11.3	0.9
	6000	8209.17	10893.6	14890.4	9,551	1,898	104.977	99.047414	19.9	0.9

Figure 4: Human RORg Inverse Agonist Assays.

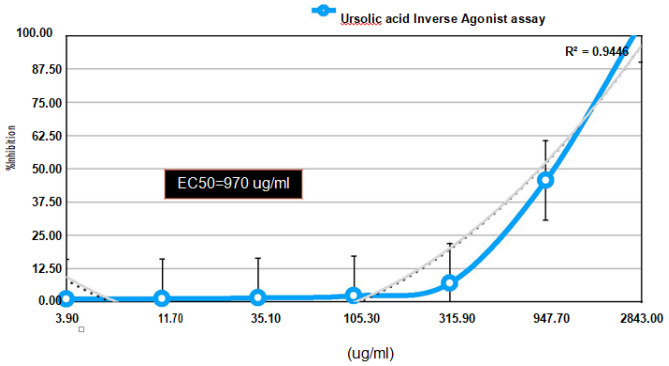

Figure 5: Result of assay of standard Ursolic acid Inverse Agonist Assay.

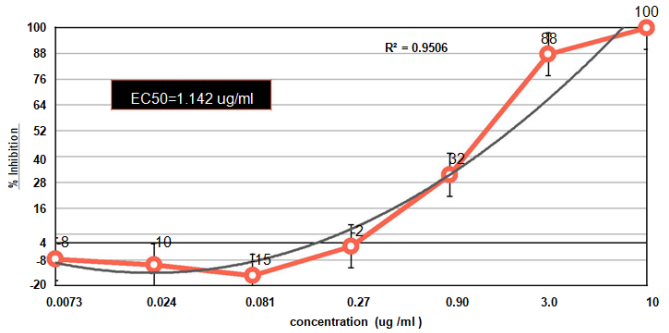

Figure 6: Metadichol Inverse Agonist assay.

Psoriasis case no. 2

Male 48, Psoriasis for 2 years was treated with Metadichol orally in mouth and on the elbow. Based on the number of bottles used, the averaged dosage was approximately about 20 mg per day (Figure 8).

Psoriasis case no. 3

Female 55, Psoriasis of hand for 2 years was treated by applying Metadichol spray for 8 weeks @ 5 mg once a day (Figure 9).

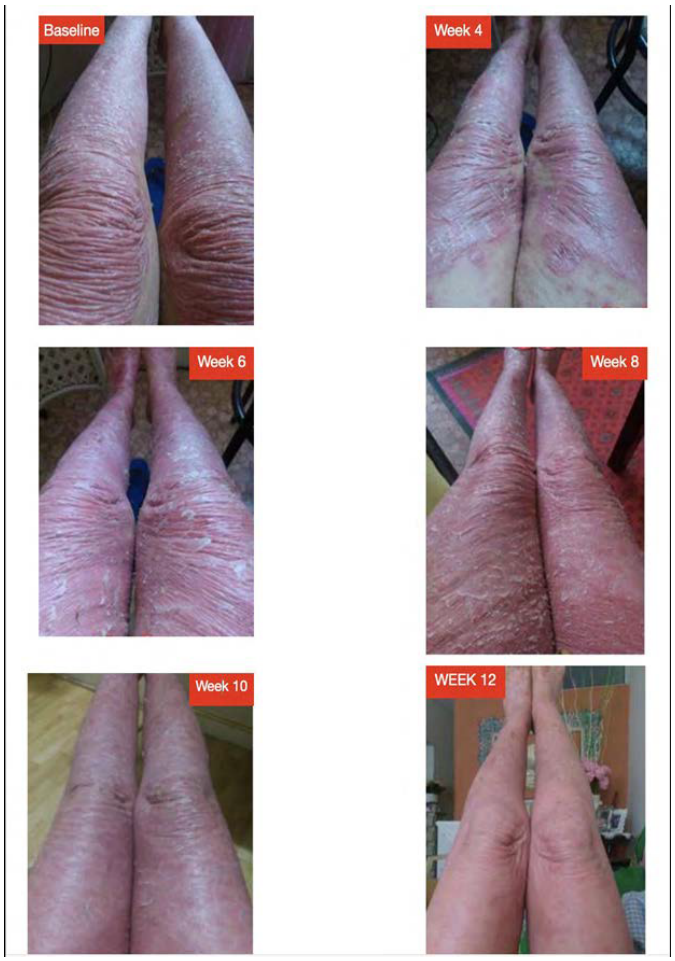

Figure 7: Case 1 representing the effect of Metadichol on 62 years female psoriasis patient.

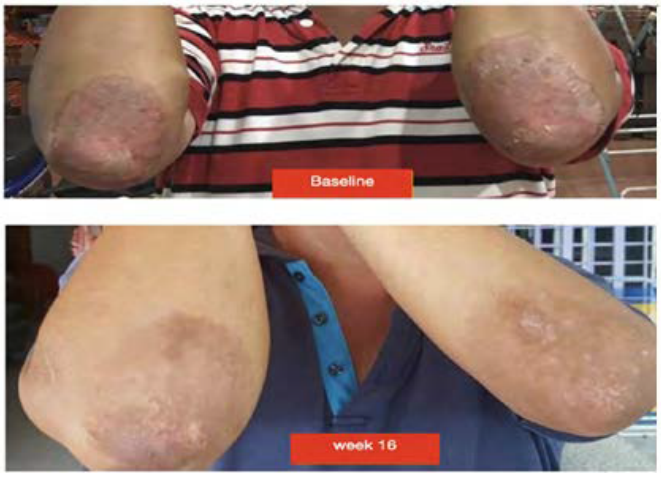

Figure 8: Case 2 representing the effect of Metadichol on 48 years male psoriasis patient.

Psoriasis case no. 4

Female 45, Psoriasis of hand was treated with Metadichol spray @ 5 mg twice a day for 4 weeks (Figure 10).

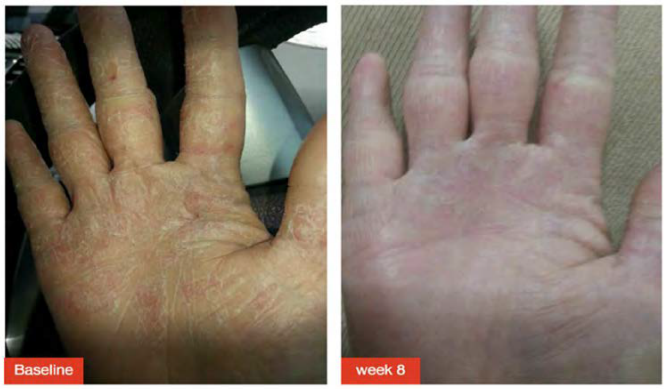

Figure 9: Case 3 representing the effect of Metadichol on 44 years female psoriasis patient.

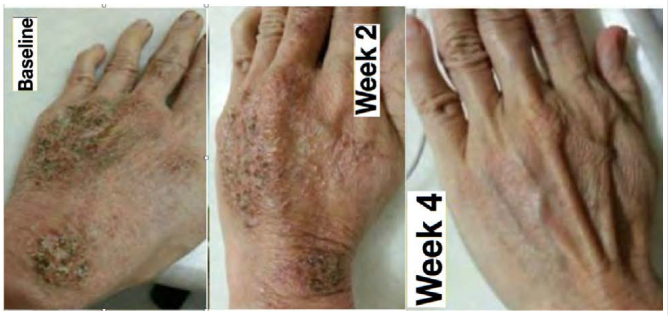

Figure 10: Case 4 representing the effect of Metadichol on 45 years female psoriasis patient.

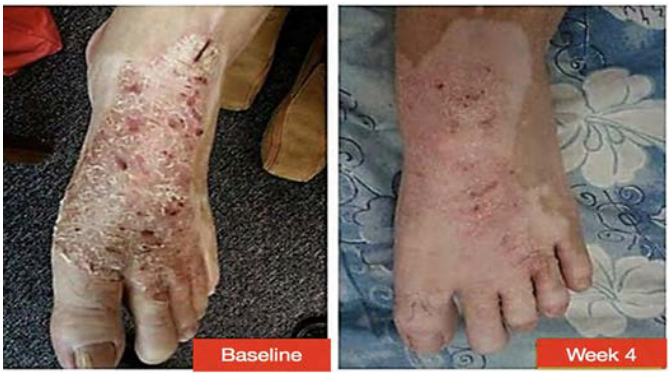

Figure 11: Case 5 representing the effect of Metadichol on 58 years male psoriasis patient.

Psoriasis case no. 5

Male 58, Diabetic patient with Psoriasis skin condition for 5 years on his leg. Applied Metadichol 5 mg orally and spray on wound area 5 mg per day for 4 weeks (Figure 11).

Psoriasis case no. 6

Male 38 with Psoriasis in nails and whole body started 5 years ago and progressively worsened. It first started in his scalp and on back, then spread to all over his body, legs, back and nails. He tried all kinds of medications but they failed to resolve his psoriasis. He started Metadichol orally 5 mg twice a day and also applied skin oils to prevent

dryness. After 24 weeks, his psoriasis has healed significantly (Figures 12-16).

Case presentation 7

17 year old, female, psoriasis related skin condition for over 12 years at age 5 started applying topical steroids with oatmeal preparations. Symptoms got Rrelieved to some extent as long as topical steroids continued, stopped topical steroids completely resulting in associated steroid withdrawal symptoms like skin blisters and thickening. She began taking symptomatic anti-Histamines when needed. (once or twice a week). She started Metadichol spray orally twice a day (10 mg). Anti-histamines continued when needed once or twice a week. With use of Metadichol, Skin started improving; thickening disappeared from most parts after 8 months Scaling stopped after 8th month. Need for anti-histamines tablets reduced to occasional use (once or twice a month) after 8 months and completely off anti-histamines at 10th month. Normal skin and hair growth on skin after 10 months. Today she is back to normal diet without restrictions (Figures 17-19).

Results and Discussion

The improved patient's symptoms presented to suggest that

Figure 12: Case 6 representing the effect of Metadichol on nails of 38 years male psoriasis patient.

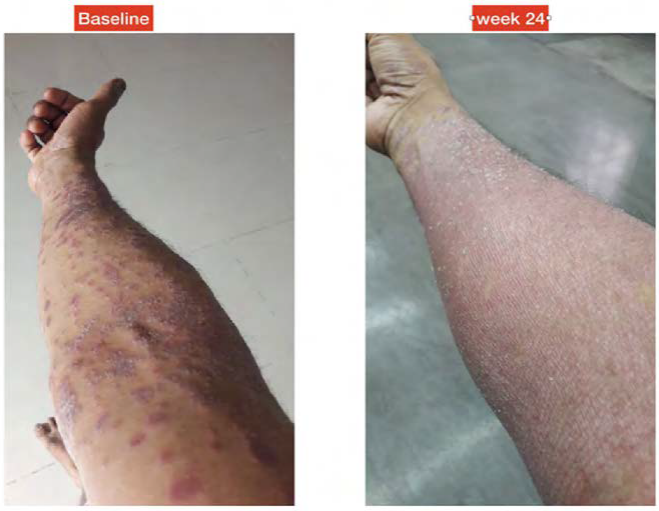

Figure 13: Case 6 representing the effect of Metadichol on hands of 38 years male psoriasis patient.

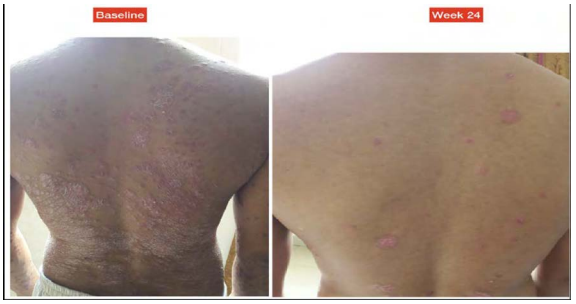

Figure 14: Case 6 representing the effect of Metadichol on back of 38 years male psoriasis patient.

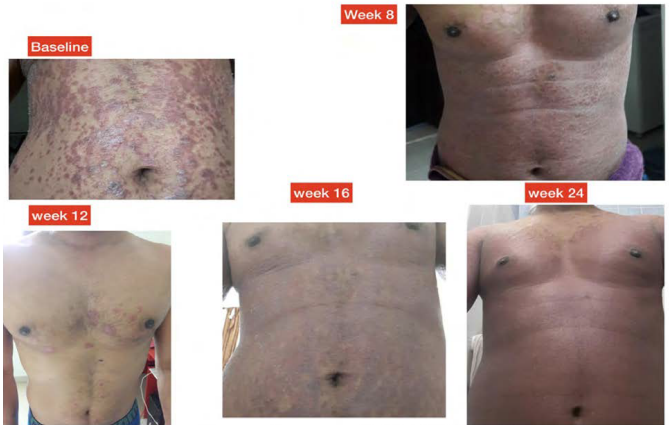

Figure 15: Case 6 representing the effect of Metadichol on the chest of 38 years male psoriasis patient.

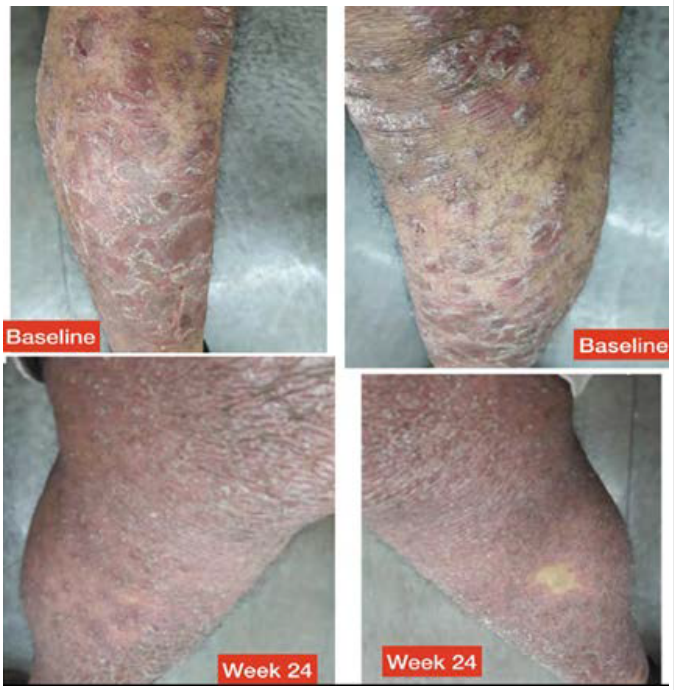

Figure 16: Case 6 representing the effect of Metadichol on the legs of 38 years male psoriasis patient.

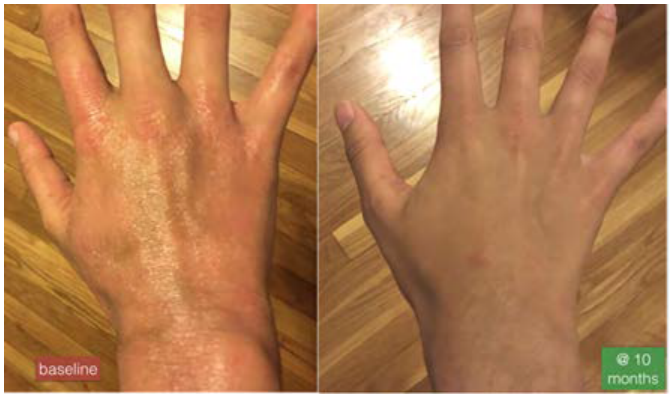

Figure 17: Case 7 representing the effect of Metadichol on the hands of 17 years female with psoriasis related skin condition.

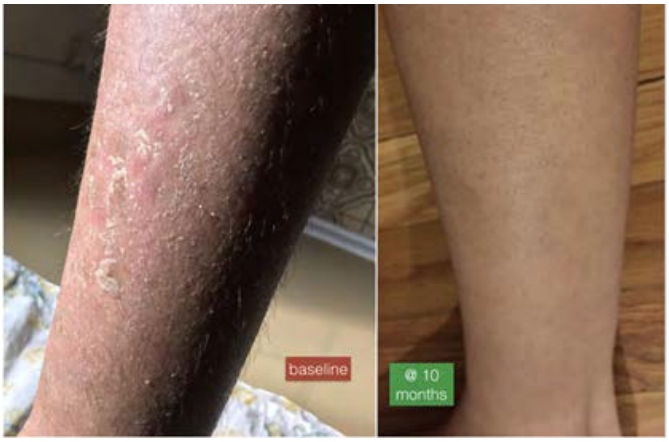

Figure 18: Case 7 representing the effect of Metadichol on the legs of 17 years female with psoriasis related skin condition.

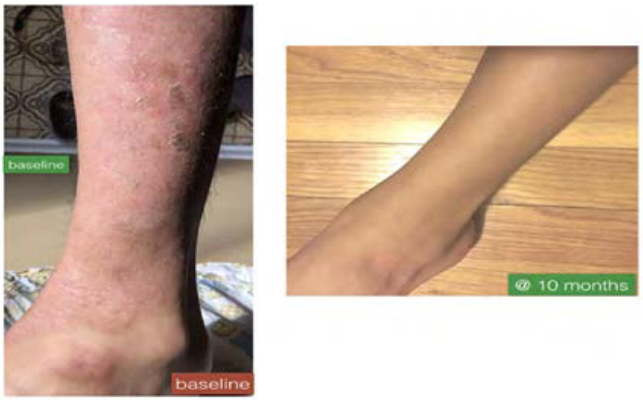

Figure 19: Case 7 representing the effect of Metadichol on the feet of 17 years female with psoriasis related skin condition.

treatment with Metadichol significantly improves their skin condition and all patients also reported that their arthritic pain had decreased. The application of Metadichol in all the cases presented, and rapid resolution of the lesions suggests that Metadichol could be modulating diseases through multiple pathways:

Metadichol binds to VDR and activates innate immunity pathways and also Inhibits TNF-α

Psoriasis can be treated by use of topical Vitamin D preparations [29]. 1-25-dihydroxy vitamin D3 (calcitriol) is the hormonally active form of Vitamin D and by binding to vitamin D receptor (VDR) modulating cellular function activates the transcription of genes that influence growth, differentiation, and inflammation in keratinocytes. On keratinocytes [30,31]. VDR binding has beneficial effects on Psoriasis, a Th1-mediated inflammatory disease, and are associated with psoriatic arthritis, Cytokines of the Th1 pathway such as TNF alpha predominate in psoriatic plaques leading to a chronic inflammatory state and formation of psoriatic skin lesions [32]. Metadichol binds to VDR and is also a TNF alpha inhibitor leading to an anti-inflammatory and anti-proliferation state to resolve Psoriasis. High anti-proliferative or anti-inflammatory acting vitamin D analogs that exert only minor calcemic activity have not been achieved to date. New agents like Metadichol that are nontoxic activate selective vitamin D signaling pathways herald a new era in dermatologic therapy and be useful in the topical treatment of various inflammatory skin diseases including atopic dermatitis and also cutaneous malignancies, such as lymphomas, squamous cell carcinoma or basal cell carcinoma. Vitamin D has an essential role in metabolic syndrome and improves psoriatic skin lesion. Psoriasis-associated co-morbidities metabolic syndrome. We have documented that Metadichol also effects key markers of the Metabolic syndrome metabolic disorders like diabetes hypertension and hyperlipidemia and obesity [33].

Metadichol inverse agonist activity against ROR gamma

By minimizing the impact of expression of Th17-type cytokine expression through its inverse agonist activity on RORγt Metadichol leads to improved clinical outcomes for patients. Th17 cytokine production is the primary driver of inflammation in plaque psoriasis. IL-17-targeting biologics have managed to reduce the disease burden of psoriasis patients. Th17 cells secrete interleukin 22, which is involved in keratinocyte differentiation retardation leading to keratinocyte proliferation [34]. On the skin, the stratum corneum layer prevents penetration of large molecule weight proteins, including monoclonal antibodies. A small molecule like Metadichol as alternative topical medicine with biologic like efficacy targets RORγt, the master regulator of IL-17 family cytokines, thus leads to improved clinical outcomes desired in Psoriasis patients. Recent data suggest that topical treatment limits Th17-type cytokine expression with clinical candidates like GSK2981278 could lead to improved health outcomes for patients [35].

Metadichol inverse agonist activity against AhR

Activation of AHR by a ligand during TH17 cell development markedly increases the proportion of TH17 and their production of cytokines. AHR, in addition to promoting the expression of IL-22, enhances TH17 cell development and the expression levels of IL-17A and IL-17F and consequently increases autoimmune pathology. These are shut down by the inhibition of AhR by Metadichol.

Summary and Conclusion

Figure 20 shows how Metadichol by acting on Nuclear receptors VDR, AHR, and ROR gamma is operating through multiple pathways to block TH17, TH1, IL17, IL22 and IL 23 pathways and thus enhancing anti-inflammatory pathways leading to resolution of psoriasis and related skin diseases. Given the safety profile of Metadichol [36,37,38].

Based on the experimental finding of Metadichol binding to the

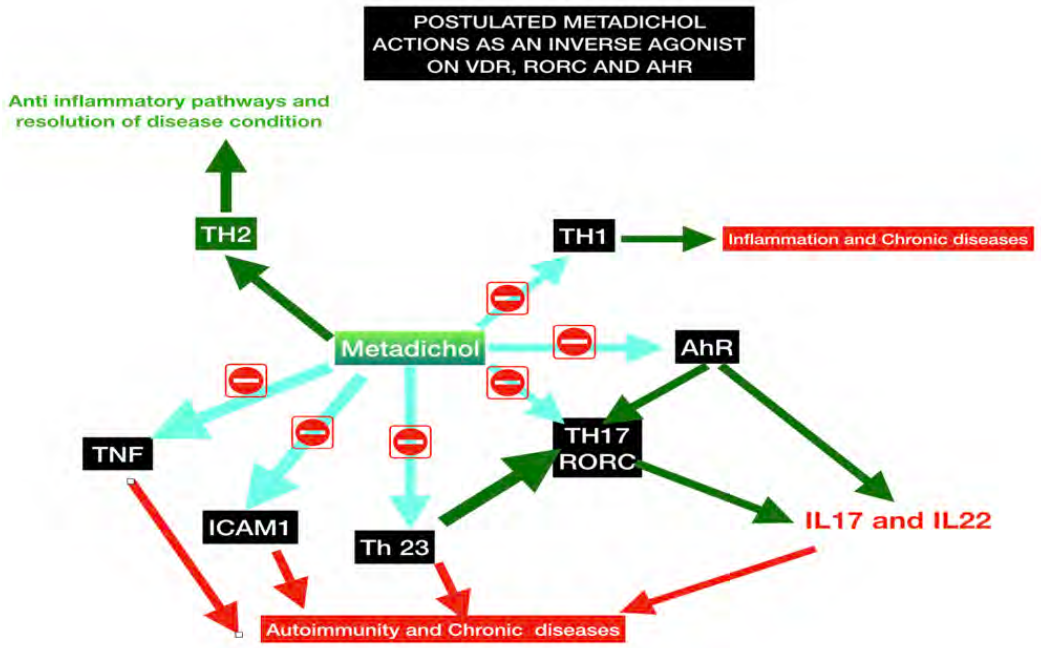

Figure 20: Metadichol action on nuclear receptors and its pathway.

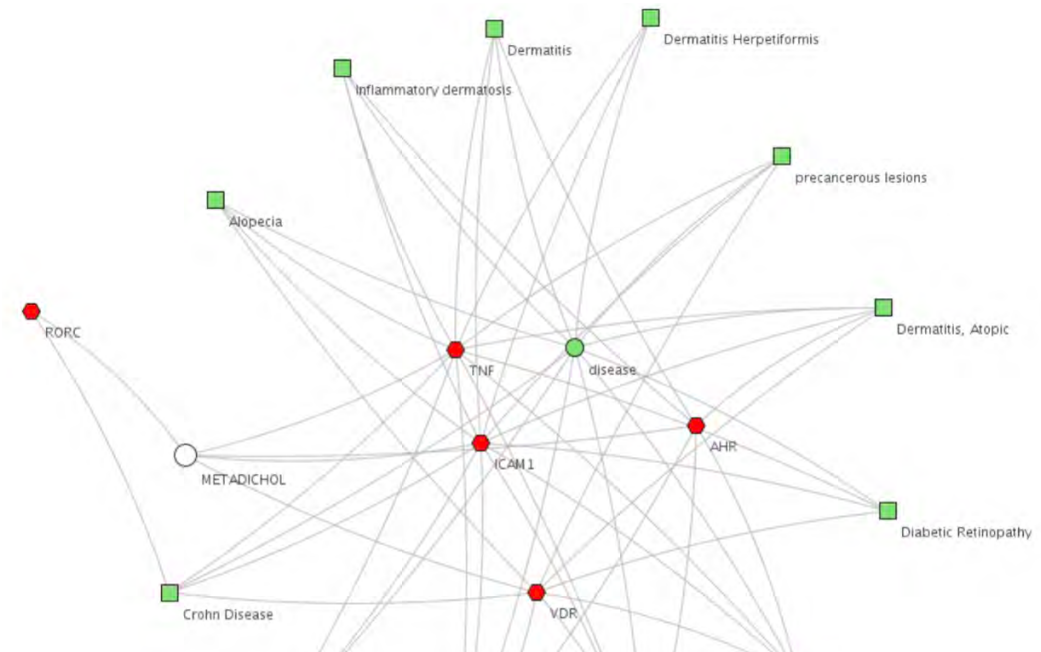

Figure 21: Metadichol targeting multiple pathways and multiple diseases that confirms the importance of network pharmacology.

receptors that have a role in Psoriasis a software program like Topp Cluster [39,40] show that these clusters of genes target many skin related disease as shown in Figure 21. All Diseases are connected through networks, and their complexity suggests that there is a need to modulate multiple targets for a superior therapeutic effect compared to ligands focused on a single target. The network-based approach is commonly called poly pharmacology [41]. Metadichol represents the first of a class of safe therapeutics that targets multiple pathways and multiple diseases that confirms the importance of network pharmacology [42-53].

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