

Metadichol® and Healthy Skin: One Approach many Possible Cures

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Abstract

Metadichol® a nano formulation of long-chain lipid alcohols derived from food. It is an inverse agonist of Vitamin D Receptor (VDR), Aryl Hydrocarbon Receptor (AHR), and Ror Game (RORC) that could have beneficial effects on skin diseases. We now present case studies of patents with various skin disease show Metadichol is an inverse agonist of these nuclear receptors thus modulating Th1 pathway towards a TH2 and Th 17 and IL 17 and IL22 and also being a TNF alpha inhibitor can modulate IL23 thus blocking the major pathways that exacerbate many Skin diseases.

Metadichol is the first molecule successfully navigates around the problems involved with promiscuous ligands and targets. It fulfils the goals of the emerging field of Poly pharmacology, i.e. a single drug is able to bind to multiple targets beyond the “one drug, one target” philosophy. We show how Metadichol is an innovative treatment for treating multiple skin diseases eczema, acne, diabetic wounds and viral and bacterial infection and also improving skin texture. Metadichol® is a safe nontoxic low cost solution and is an alternative to numerous clinical candidates in combating over 3000 skin diseases.

Keywords: Metadichol; Psoriasis; Eczema; Acne; Warts; Diabetic wounds; VDR; Vitamin D; Calcitriol; Inverse agonist; TH1; TH2; ROR gamma T; (RORγt); Interleukin (IL)-17; IL-23; Tumor necrosis factor (TNFα); IL-17-producing T (T17) cells; T helper (Th)1 cells; Th22 cells

Introduction

The skin is the largest organ of the body that fulfills multiple essential tasks. It forms the boundary between the inside and outside. It protects against mechanical and chemical threats, it provides innate and adaptive immune defenses, it enables thermoregulation and vitamin D production, and it acts as the sensory organ of touch [1].

Skin is frequently damaged because it is directly in the ‘firing line’ and, skin diseases are widespread. Skin diseases are a significant cause of global disease burden, affecting millions of people worldwide. There are more than 3000 known diseases of the skin [2]. Aging, environmental and genetic factors, and trauma can result in the development of a diverse set of skin diseases [3,4].

A cosmetically disfiguring disorder can have a significant impact and can cause considerable discomfort and disability. Most of the chronic skin diseases like atopic eczema, psoriasis, vitiligo and leg ulcers, are not immediately life-threatening but are an enormous burden on health status and quality of life issues, physical as well as mental. One in four Americans (85 million) Million Americans were seen by a physician for skin disease in 2013. In 2013, skin disease resulted in direct health care costs of \$75 billion and indirect lost opportunity costs of \$11 billion. Another study estimated the cost of Psoriasis alone in the US to be \$112 billion [5].

Skin diseases become more prevalent as population ages worldwide [6], which directly affects the overall health (Figure 1). A wellness and prevention approach to protecting the skin can substantially reduce the incidence of non- melanoma and other skin cancers [7]. Maintaining a healthier skin enables better health outcomes leading to a more active and engaged lives.

There are many Biologic agents used today to treat different cutaneous diseases. Antibiotics like Tetracycline, Rifampicin Retinoids like Acitretin, Anti-androgens like Metformin and Spironolactone and immunosuppression drugs like Cyclosporine. Some mAbs are in in use for psoriasis, atopic dermatitis, melanoma, and other skin diseases target IL-17 and TNF alpha [8,9]. Many promising target therapies are

Some common skin diseases			
Acne	Contact dermatitis	Nonmelanom a skin cancer	Viral HSV/HZV
Actinic damage	Cutaneous infections	Pruritus	Fungal diseases
Atopic dermatitis/eczema	Cutaneous lymphoma	Psoriasis	Vitiligo
Noncancerous skin growths benign, scars/cysts	Drug eruptions	Rosacea	Wounds and burns
Bullous diseases	Hair and nail disorders	Seborrheic dermatitis	Rosacea
Melanoma	HPV / warts	Ulcers	Seborrheic dermatitis

Figure 1: Representation of International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes.

under study, including bio similars, reduce costs burden associated with these originator monoclonal antibodies. Despite progress in research in the dermatologic field, a more through pathophysiology of diverse skin conditions is needed to target 3000 skin diseases with a cheaper and cost-effective solution (Figure 1).

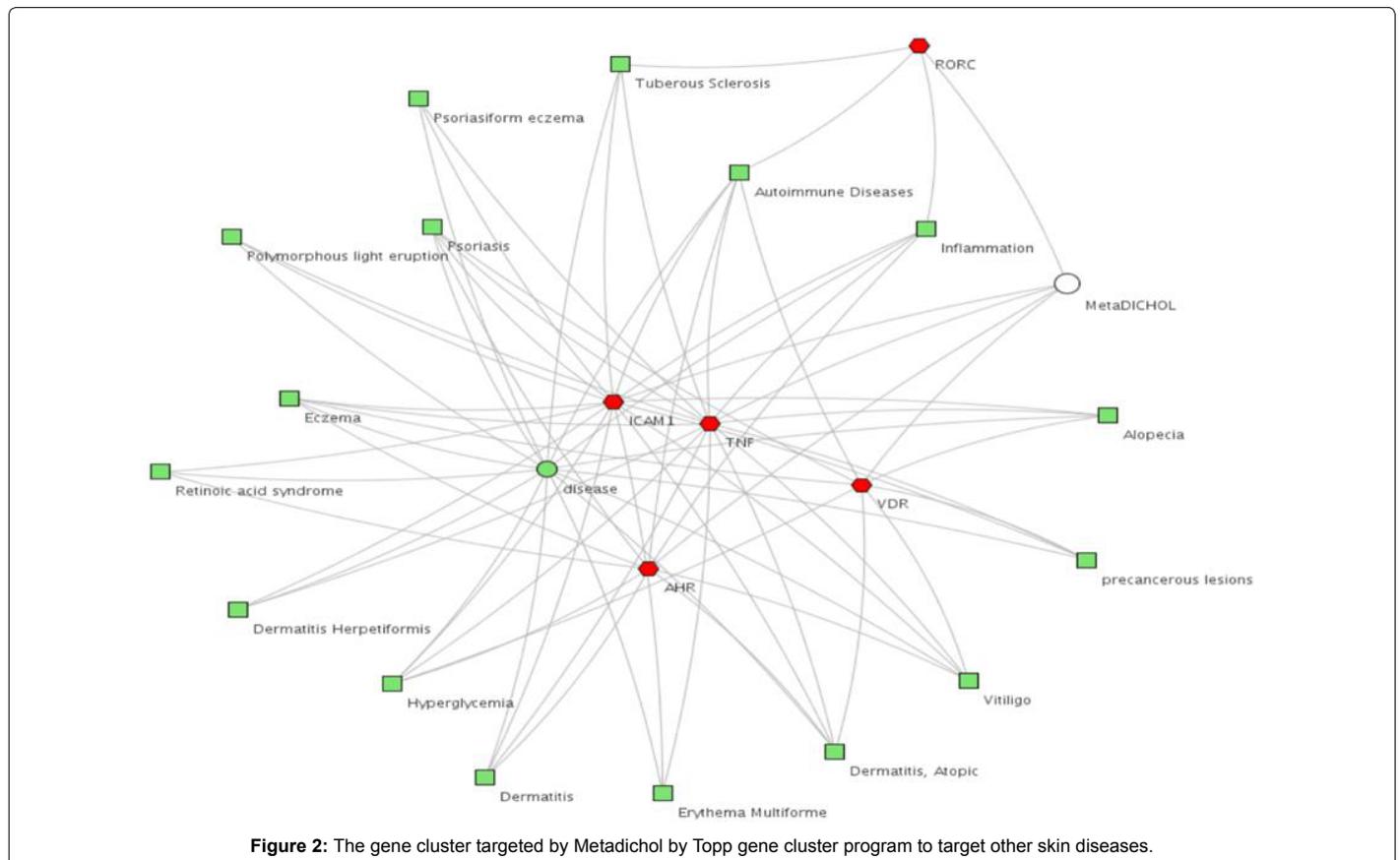
Metadichol [10] is a nano used lipid formulation of long-chain naturally alcohols. It is inverse agonist of VDR (Vitamin D receptor) AHR (Aryl hydrocarbon receptor), RORC (Retinoic acid receptor gamma) and a TNF alpha inhibitor. We have recently documented how Metadichol is effective against Psoriasis [11]. The gene cluster targeted by Metadichol above are predicted by Topp gene cluster program [12] to target other skin diseases as shown in Figure 2. One can also see that Skin diseases are related to each other as predicted by Disease Connect [13], which is based on curated experimental data as shown in Figure 3

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with a p-value less 10^{-9} . Given this high degree of correlation predicted. We decided to test this hypothesis below by treating Metadichol on patients with various skin diseases.

Case Studies

Presented are case studies related to skin diseases. Metadichol (5 mg/ml) is sprayed on the affected area and or taken orally. In some cases, Metadichol gel is used the concentration was 2.5 mg/gm and applied to affected areas (Figures 4-38).

Results and Discussion

The results confirm the theoretical prediction as show in Figures 1 and 2. The clinical case studies presented suggest that there is a common pathway through which Metadichol that seems to act to mitigate the condition be it eczema or viral skin disease like herpes or diabetic wound healing and also skin rejuvenation. Metadichol binds to Vitamin D receptor (VDR) as an inverse agonist and seems to mimic the well-known actions of 1,25 dihydroxy Vitamin D3 (Vitamin D3) the natural signs of VDR. The effect of 1,25(OH)₂ D3 are mediated by its binding to the vitamin D receptor (VDR). Once it binds its ligand, VDR dimerizes with a RXR (retinoid X receptor). These VDR-RXR hetero-dimers bind to vitamin D response elements present on target genes [14-16].

In addition to transcriptional activation, the hetero-dimers can displace the nuclear factors of activated T cells resulting in repression of cytokine-related genes [17].

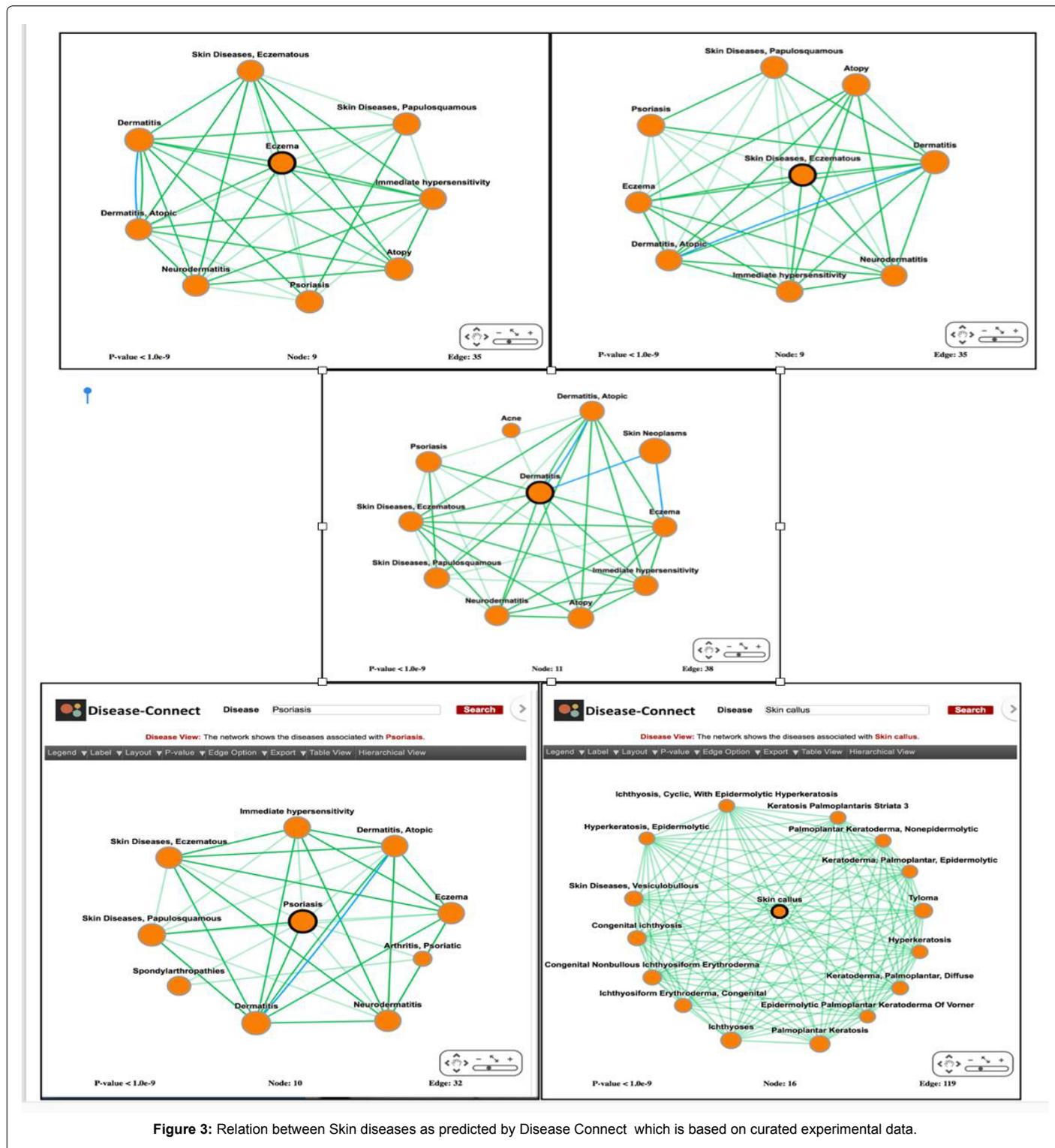
1,25(OH)₂ D suppresses Th-1 cell proliferation leading to the

lowered production of interferon gamma and interleukin-2 [18-20]. Lower levels of circulating cytokines leads to less antigen presentation by dendritic cells, in addition to less T lymphocyte recruitment and proliferation. Expression of Th-2 associated cytokines, including interleukin-4 are increased by 1,25(OH)₂D₃. Overall, vitamin D polarizes the adaptive immune system away from Th-1 and toward Th-2 responses Th cells influenced by vitamin D are interleukin-17 (IL-17)-secreting T cells (Th17 cells). Also, Vitamin D3 suppresses IL-17 production via direct transcription and suppression of IL-17 gene expression [21].

The majority of these studies indicate an inverse relationship between the severity of atopic dermatitis and vitamin D levels. Individuals with AD treated with vitamin D resulted in decreased severity of the disease [22,23].

Acne vulgaris is a skin disorder affecting millions of people worldwide. Inflammation resulting from the immune response targeting *Propionibacterium acnes* (*P. acnes*) has a significant role in acne pathogenesis. It has been demonstrated that *P. acnes* are a potent inducer of Th17 and that 1,25(OH)₂D inhibits *P. acnes*-induced Th17 differentiation, and thereby could be considered as a useful tool in modulating acne [24].

Herpes and shingles are caused by herpes family of viruses, which can establish infections that lay dormant and then can reactivate under certain conditions. Herpes simplex virus-1 (HSV-1) and herpes simplex virus-2 (HSV-2) can cause oral and genital herpes. Varicella-zoster virus results in chickenpox in children and shingles later in life. The anti-viral effects of vitamin D could be explained by cathelicidin (in



the form of LL-37), human beta-defensin 2, and perhaps through the release of reactive oxygen species [25].

Vitamin D has an essential role in innate immune response modulation. The toll-like receptors (TLRs) in macrophages, polymorphonuclear cells, monocytes, and epithelial cells are central to the innate immune response [26,27]. TLRs recognize pathogen-

associated molecular patterns associated with infectious agents. TLR2 recognizes the lipopolysaccharides of bacteria and also the viral proteins and nucleic acids. Upon recognition, activated TLRs release cytokines that induce expression of antimicrobial peptides and reactive oxygen species. Metadichol has been shown to be active against MRSA bacterial infection [28].



Figure 4: Female-45 with eczema on her right hand for more than ten years. She had tried many medicines and topical drugs but with no success. Treated with Metadichol Nano-Spray in the mouth and on hand for 8weeks. Her hand eczema has completely healed.



Figure 6: Female aged 18 years old with Eczema for six years was started treatment by spraying leg with Metadichol. Healed in 4 weeks.

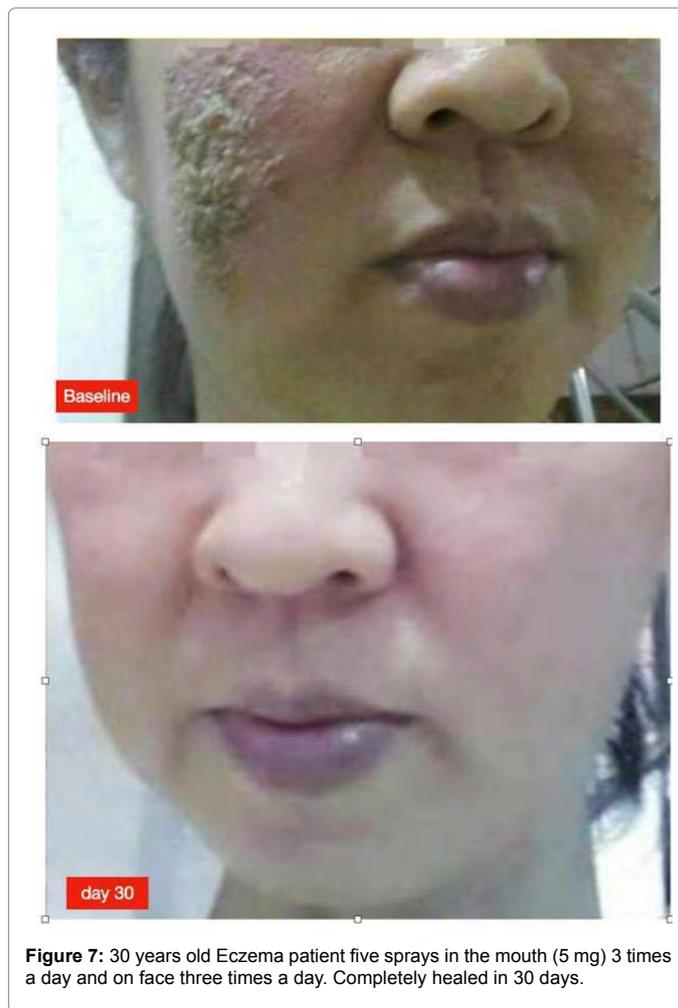


Figure 7: 30 years old Eczema patient five sprays in the mouth (5 mg) 3 times a day and on face three times a day. Completely healed in 30 days.



Figure 5: A 12 years old girl with painful eczema under her left foot for a year. Treated by doctors with different cream and drugs but with no success. Had difficulty walking. Treated with Metadichol by spraying (5 sprays a day) in the mouth and on eczema three times a day. Day 10 her eczema foot healed to the extent and was able to walk without any discomfort or pain.

Skin wounds require vitamin D3 to protect against infections initiate the normal repair process. Vitamin D has an indirect role in wound healing due to its effect on improved glycemic control or 12 weeks among patients with diabetic foot injury had beneficial effects inflammatory markers like ESR, hs-CRP [29]. Vitamin D deficiency



Figure 8: Male 40 Eczema of hand Applied gel on affected areas twice a day.



Figure 9: Male 40 Eczema of hand. Sprayed Metadichol on the affected area. Conditions cleared in 7 days.

compromises the body's innate immune system, making a patient more vulnerable to microbes and infections [30]. Vitamin D3 role in innate immunity is to enable keratinocytes to recognize and respond to bacteria and to protect wounds against infection [31] Metadichol as we documented has a powerful effect on diabetic patients [32,33]. Metadichol is an agonist of GPR 120 [34]. This is another pathway through which it can act as shown by Arantes El et al. [35] that the topical use of GPR 120 agonists like polyunsaturated fatty acids (PUFAs) can accelerate skin wound healing. Da Younz et al. [36] have shown that GPR120 agonist treatment of high-fat diet-fed obese mice causes improved glucose tolerance, decreased hyperinsulinemia, increased insulin sensitivity and decreased hepatic steatosis. For wound healing, a decrease in glucose levels leads to improved outcomes.

Atopic Dermatitis (AD) is a common chronic inflammatory skin disease where VDR signaling is essential to be important not only in

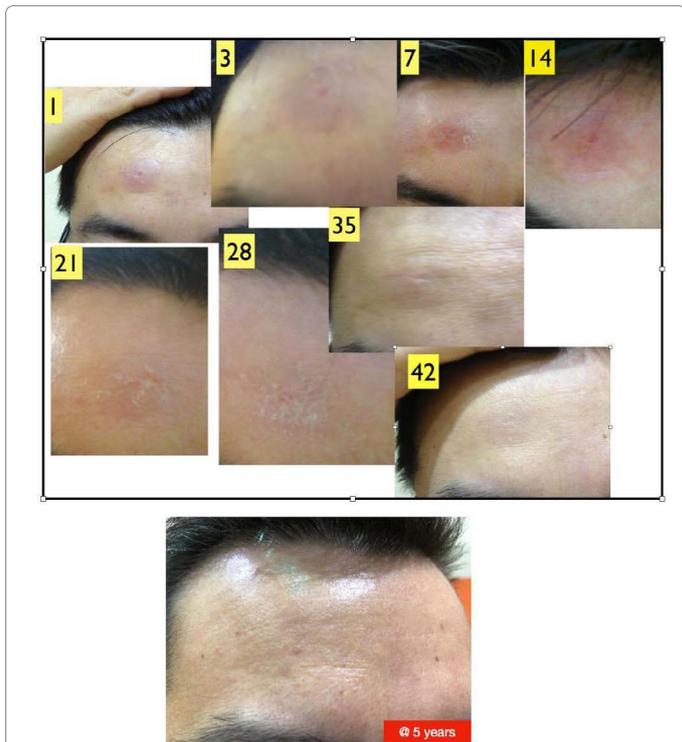


Figure 10: Male 36 years old with eczema. Progress with Metadichol gel day 1 to 42. Gel treatment stopped. After five years no recurrence.



Figure 11: M-50. Type 2 diabetic for ten years. Left index toe was amputated. Sprayed Metadichol on affected area 3 times a day and 5 mg per day orally.



Figure 12: Female 61. The diabetic wound on feet did not heal over two years could not walk. Metadichol sprayed on wound three times a day. Now walks slowly with the heel raised without pain.

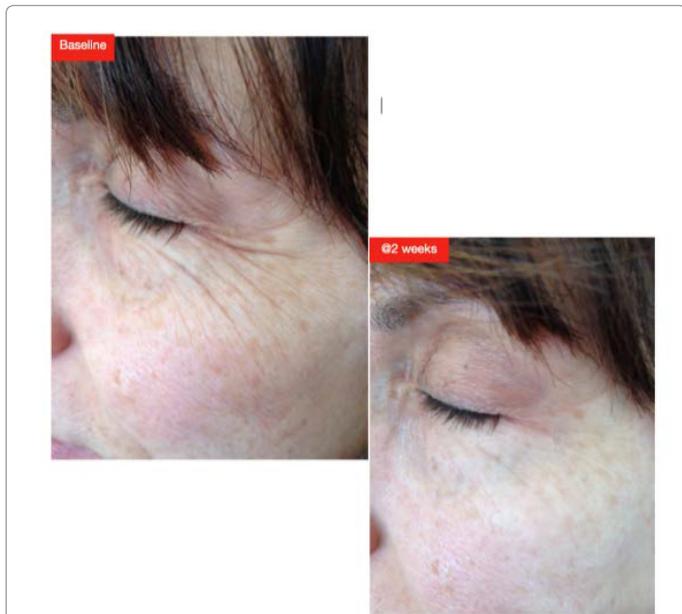


Figure 13: Female 83 diabetics for 25 years. Left foot was amputated at age 76. Right foot has a diabetic wound that did not heal. Treated with Metadichol for two months. The diabetic wound on right foot healed.

the immune system but also in particular keratinocytes to regulate skin homeostasis and epidermal barrier function. Hartmann et al. [37] showed that regulatory T cells have a role in the AD, are increased in the skin of VDR agonist-treated mice and induction of skin barrier gene and antimicrobial peptide gene expression in skin lesions of the treated

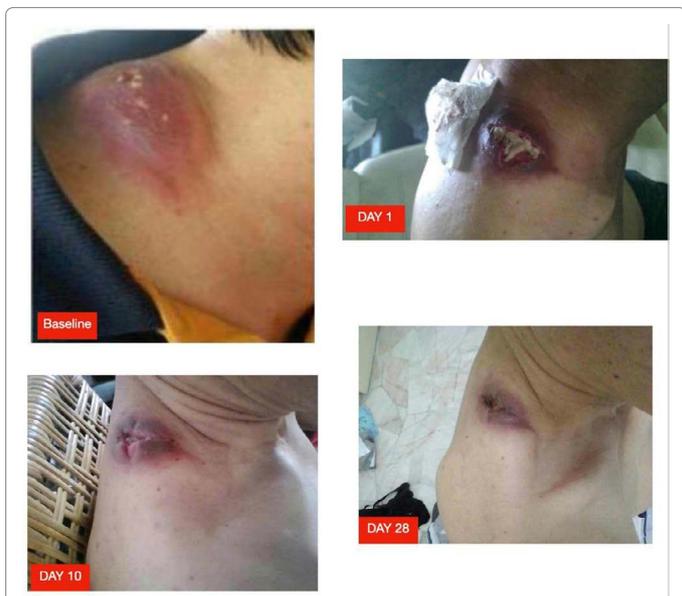


Figure 14: Wound healing Metadichol 5 mg per day orally and sprayed on wound Middle-aged man with a painful tumor on his neck for over 20 years. A diabetic, his tumor could not be operated. After using Metadichol, the tumor pain was gone within 30 minutes. Yellow pus and blood discharged after a day during the first two weeks. After using Metadichol for one month, the wound is almost healed.



Figure 15: Diabetic Wound-Calf. Subject: Female-52. Had wound for more than six months. It started as a small spot and was prescribed Calapure by a physician. The patient stated the wound always bleed after a hot bath. When scratched, it begins to look very "angry" and red. Metadichol topically and orally twice a day.

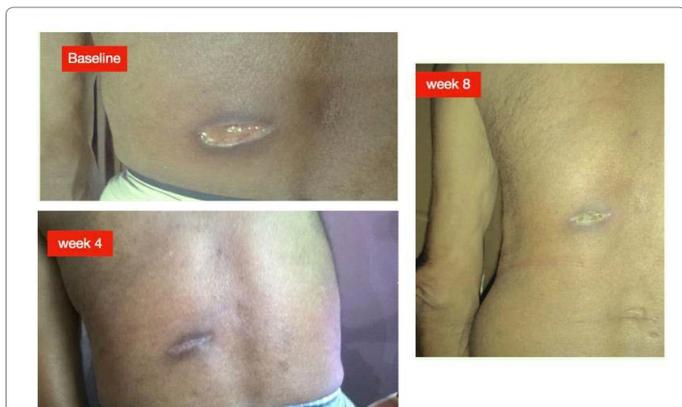


Figure 16: Patient M-65. Carbuncle is a cluster of boils, which drains pus onto the skin. It is usually caused by bacterial infection, most commonly with *Staphylococcus aureus* or *Streptococcus pyogenes*, which can turn lethal. Diagnosed and treated with antibiotics for one year without improvement. Metadichol @ 5 mg per day sprayed on the wound.

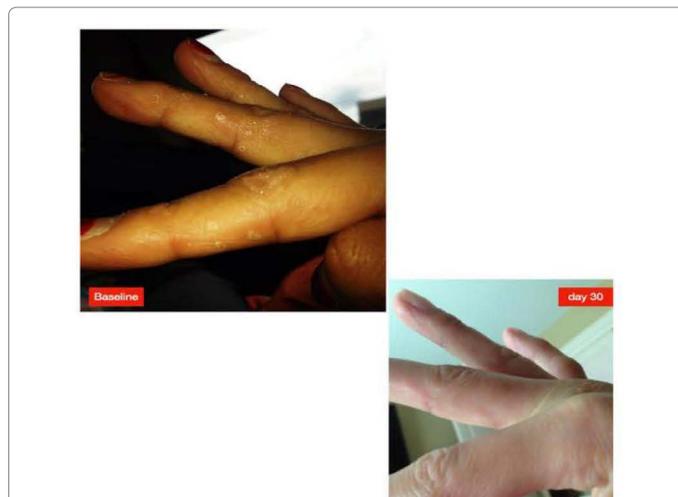


Figure 19: WARTS. Female, 33 years old. Warts on the palm of hands and fingers. She experienced a sudden outbreak of warts on her hands due to an immune response to toxins in the body. Over 50, dry and rough spots were developing into warts on all fingers: Tiny, brown specks appeared all over palms and fingers, forming into wart heads. Small, circular-shaped spots were scaly and dry. These spots were the beginning of wart heads forming: Over 50, dry and rough spots were developing into warts on all fingers: She noted it looked like small coffee grinds all over palms: Treated by spraying Metadichol on each hand, two times per day. Orally, two sprays (2 mg) per day.



Figure 17: Male-45 Herpes on his back and stomach. Sprayed with metadichol.



Figure 18: Male 34 fungal infection and skin were peeling painful while walking. Pain eased after day1.

mice. Targeting the VDR with low-calcemic agonists is being explored as a new feasible approach for the AD.

Alopecia results when the immune system attacks the hair follicles, resulting in patterned hair loss. Cianferotti et al. found that vitamin D receptors in the hair follicles play a role in normal hair cycling loss [38]. Mutation of the VDR, in humans and mice, results in alopecia. The actions of VDR that prevent alopecia are ligand-independent.



Figure 20: Male, ten years old. Condition: Keratosis Pilaris, Eczema and toe injury scrape from swimming pool. Topically, spray twice a day on the affected area. Rash and inflammation decreased. Scabs faded to healthy skin.



Figure 21: Hand Foot Mouth Virus (HMF). Female, 35 years old contracted HMF virus mostly on hand from her son (see figure 22). She developed red itchy sores on her hands. She was severely allergic to Benadryl. Metadichol Topically and orally 4 times per day.

Mutations in the VDR that disrupt the ability of the unliganded VDR to suppress gene transcription are hypothesized to lead to disruption if the hair cycle that ultimately leads to alopecia [39]. It like hair follicle cycling is dependent on unliganded actions of the VDR [40].

Vitamin C is an antioxidant useful for preventing and treating skin aging. It stimulates the barrier function of the endothelial cells and is proven to have photo protective effects [41,42]. What hampers its uses widely is the inability to delivery into the dermis for collagen production [43].

Metadichol over comes this delivery problem as it increases



Figure 22: Hand Foot Mouth Virus - CHILD. Male five years old. Pus oozed from the sores. It was itchy and painful to the point of crying. Metadichol helped reduce the pain, relieved itching, eased the oozing sores, and stopped the spread of the lesions. Metadichol was used topically and orally up to 4 times per day. After one day of using Metadichol sores began to scab and dry out. Less itching on 5th-day, sores drying out and shrinking in size, less redness.



Figure 23: F-14 years old conjunctivitis sprayed Metadichol into eye at 24 h the area around eye turned red and at 36 h completely cured and clear.



Figure 24: Shingles Patient. F-62 Metadichol sprayed on the affected area and orally @ 5 mg per day.



Figure 25: Patient M-58 ganglion cyst that he could not rid with surgery every year for two years and reappeared in days after each operation. Applied Metadichol gel and it healed in 12 weeks. Five years since last application of gel and no reappearance of Cysts.



Figure 28: M-25. Thumb Injury caused by a car door. Sprayed with Metadichol complete healing on day 3.



Figure 26: M-35. Finger wound that did not heal. sprayed with Metadichol twice a day.



Figure 29: M-65, while cooking spilled hot oil on his hand. Treated with Metadichol sprayed twice a day on affected areas.



Figure 27: M-30. Deep Laceration on the arm and Metadichol sprayed on affected areas twice a day.



Figure 30: Male 85 bed sore infection in Hospital. Gel applications on the affected area. Complete healing on 3rd day.



Figure 31: Female 35. Dog bite. Sprayed Metadichol on affected area.



Figure 33: F-58 years old. Skin treatment with Metadichol Gel twice a day.

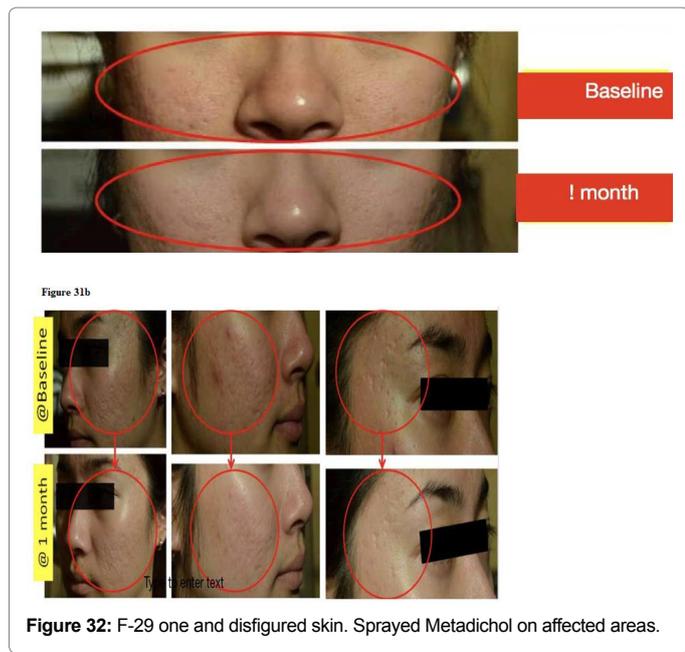


Figure 31b



Figure 32: F-29 one and disfigured skin. Sprayed Metadichol on affected areas.



Figure 34: F-24. Pimples and acne and disfigures skin.



Figure 35: F-36 acne and pimples. Metadichol gel twice a day and vast improvement in skin seen after three days.

Vitamin C levels [44,45] over and beyond what is achieved by oral supplementation. Vitamin C is present at cutaneous level, displaying antioxidant, anti-inflammatory, photoprotective properties, and is a known bio stimulator of collagen synthesis [46]. It has a role in the maintenance of dermal collagen, preventing the inactivation of enzymes involved in the biosynthesis of collagen, hydroxylase, and lysine [47].

Vitamin D3 has an essential role in mitigating many skin diseases be it production of AMP's, Th 17 inhibition and directing immune response towards a Th2 outcome [48]. Metadichol binds to VDR as an inverse agonist and based on the result mimics the action of Vitamin D3. Also, its effects are enhanced by its inverse agonist actions on RORC that is involved in the Th17 expression.

Metadichol also is an inverse agonist of AHR which is involved

in adaptive responses against UVB or topical chemicals and plays a role in maintaining homeostasis of skin cells and skin immunity. AHR ligands have applications in the prevention and treatment of skin disease [49].

Further Metadichol is an inhibitor of TNF alpha a significant cytokine of inflammatory diseases of the skin. The anti-TNF alpha arsenal is currently dominated by Etanercept, a fusion protein



Figure 36: Male 35. Cut with a knife that needed 20 stitches. Scar did not go after one year. Applied Gel and most of the ugly scar disappeared and new skin formation.



Figure 37: M-25 with a wound on arm. Metadichol gel applied on affected area led to elimination of skin marks.



Figure 38: Female 17 with eczema since she was a baby. Treated with Metadichol orally and on skin. 4 days later, her eczema spots are healing.

composed of a soluble TNF alpha receptor, and infliximab, a chimeric monoclonal antibody. Many dermatological diseases will probably benefit from these new treatments. These promising new treatments, although expensive, and with yet unknown long-term side effects, A small number of Studies have already demonstrated their interest in cutaneous and articular psoriasis. Encouraging sporadic results suggest other potential indications of Behcet's disease, bullous dermatitis, neutrophilic dermatitis, toxic epidermal necrolysis, and systemic vasculitis [50].

Metadichol is also an inhibitor of ICAM 1 and expression of cell-adhesion molecules are known to contribute to inadequate inflammatory response seen in inflammatory skin diseases. The epidermis of patients with inflammatory skin diseases exhibits increased expression of ICAM 1 [51].

Conclusion

Given that there are approximately 50000 diseases [52] that confirm humanity. The dogma 'one drug', 'one target', 'one disease' is not a viable option. A Poly pharmacological approach [53-55], i.e., single drug acting on multiple targets of a unique disease pathway or a single drug working on multiple targets on multiple disease pathways is an emerging approach that needs to be exploited.

Metadichol is first in this class of molecules. It acts on varied diseases and through multiple pathways. It is also a food-based ingredient devoid of any side effects and could be the harbinger of changes that can impact the healthcare industry. Metadichol by its actions on VDR, AHR, RORC, TNF alpha and ICAM1 efficiently shuts down the many pathways that are involved in the inflammatory process in the pathogenesis of skin diseases. This explains why Metadichol is useful in many types of skin diseases based on the results we have presented. Given that there are over 3000 skin diseases and it would be virtually impossible to treat one by one, it rains hoped that molecules like Metadichol a safe food-based ingredient will fulfil the quest to reduce the burden of skin diseases worldwide.

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