Metadichol® and Healthy Skin: One Approach many Possible Cures
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Abstract

Metadichol® is 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 gamma (RORC) that could have beneficial effects on skin diseases. We now present case studies of patients with various skin diseases who has symptoms mitigated on treatment with Metadichol. The proposed mechanism is that Metadichol by its actions on the above mentioned nuclear receptors affects Th1, TH2, Th17, IL 17 and IL22 and IL 23 pathways that exacerbate many Skin diseases.

Introduction

The skin is the largest organ of the body that protects against mechanical and chemical threats, it provides innate and adaptive immune defenses, enables thermo-regulation and vitamin D production, and acts as the sensory organ of touch [1]. Skin is frequently damaged because it is directly in the ‘firing line’ and is an enormous burden on health status and quality of life issues, physical as well as mental. One in four Americans (85 million) 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].

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, Vitiligio 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. 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 dermatistis, melanoma, and other skin diseases target IL-17 and TNF alpha [8,9]. Many promising target therapies are under study, including bio-similar that reduce costs associated with these originator monoclonal antibodies. Despite progress in clinical dermatology 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 lipid formulation of long-chain naturally alcohols. It is an inverse agonist of VDR (Vitamin D receptor) AHR (Aryl hydrocarbon receptor), RORC (Reitinoic 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 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.

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

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

<table>
<thead>
<tr>
<th>Some common skin diseases</th>
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<tbody>
<tr>
<td>Acne</td>
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<td>Contact dermatitis</td>
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<td>Nonmelanoma skin cancer</td>
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<td>Viral HSV/HSVZ</td>
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<td>Atopic dermatitis/eczema</td>
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<td>Cutaneous infections</td>
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<td>Psoriasis</td>
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<td>Fungal diseases</td>
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<td>Atopic dermatitis/eczema</td>
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<td>Cutaneous lymphoma</td>
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<td>Psoriasis</td>
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<td>Vitiligo</td>
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<td>Drug eruptions</td>
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<td>Rosacea</td>
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<td>Wounds and burns</td>
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<tr>
<td>Bullous diseases</td>
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<tr>
<td>Hair and nail disorders</td>
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<tr>
<td>Seborrheic dermatitis</td>
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<tr>
<td>Rosacea</td>
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<td>Melanoma</td>
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<td>HPV/warts</td>
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<tr>
<td>Ulcers</td>
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<td>Seborrheic dermatitis</td>
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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 was 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 2 and 3. The clinical case studies presented suggest that there is a common pathway through which Metadichol acts to mitigate the condition be it eczema or viral skin disease like herpes or diabetic wound healing and 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 agonist of VDR. The effect of Vitamin 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].

Vitamin D3 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 Vitamin D3. Overall, vitamin D3 polarizes the adaptive immune system away from Th-1 and toward Th-2 responses. Also, Vitamin D3 suppresses IL-17 production via direct transcription and suppression of IL-17 gene expression [21].

The majority of studies done so far indicate an inverse relationship between the severity of atopic dermatitis, eczema and vitamin D levels. Individuals with AD and eczema treated with vitamin D led to 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 1,25OH2D 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 are generally dormant but they 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 it inducing cathelicidin (in the form of LL-37) and also human
beta-defensin 2, and the likely 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].
Skin wounds require vitamin D3 to protect against infections to initiate the normal repair process. Vitamin D has an indirect role in wound healing due to its effect on improved glycemic control in 12 weeks among patients with diabetic foot injury and reduced inflammatory markers like ESR, hS-CRP [29]. Vitamin D deficiency

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 8 weeks. Her hand eczema healed completely.

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.

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

Figure 7: 30 year 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.
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 earlier has a powerful effect on diabetic patients [32,33]. Metadichol is an agonist of GPR 120 [34]. This is another pathway though 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
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 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 17: Male-45 Herpes on his back and stomach. Sprayed with Metadichol.

Figure 18: Male 34 fungal infection and skin peeling painful while walking. Applied Metadichol gel on affected are. Pain eased after day 1.

Figure 19: 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. 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.

mice. Targeting the VDR with low-calcemic agonists could be a new feasible approach for the AD.

Alopecia results when the immune system attacks the hair follicles, resulting in patterned hair Cianferotti et al. found that vitamin D receptors in the hair follicles play a role in normal hair cycling loss [38]. Mutation of VDR, in humans and mice, results in alopecia. The actions of VDR that prevent alopecia are ligand-independent.
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 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 is an inverse agonist of AHR which is involved...
Figure 24: Patient M-58 ganglion cyst that he could not rid with surgery every year for two years and it 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 25: M-35. Finger wound that did not heal, sprayed with Metadichol twice a day.

Figure 26: M-30. Deep Laceration on the arm and Metadichol sprayed on affected areas twice a day.

Figure 27: M-25. Thumb Injury caused by a car door. Sprayed with Metadichol complete healing on day 3.

Figure 28: M-65, while cooking spilled hot oil on his hand. Treated with Metadichol sprayed twice a day on affected areas.

Figure 29: Male 85 bed sore infection in Hospital. Gel applications on the affected area. Complete healing on 3rd day.
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].

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 composed of a soluble TNF alpha receptor, and infliximab, a chimeric monoclonal antibody. Many dermatological diseases will probably benefit from these new treatments. These are expensive, with unknown long-term side effects, A small number of Studies have already demonstrated their effects 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 50,000 diseases [52] that confront 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 them one by one, Molecules like Metadichol a safe food-based ingredient will hopefully fulfill the quest to reduce the burden of skin diseases worldwide.

References


