Perillyl alcohol inhibits keratinocyte proliferation and attenuates imiquimod-induced psoriasis like skin-inflammation by modulating NF-κB and STAT3 signaling pathways

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Abstract

Psoriasis is a chronic inflammatory and proliferative skin disease characterized by pathological skin lesions which significantly impact the quality of life. Perillyl alcohol (POH) is a hydroxylated monoterpene, naturally found in essential oils like Lavandula augustifolia, Prunus avium etc. Recent studies have been proven that inhibitors of farnesyltransferase enzyme showed significant anti-psoriatic activity. POH is one such natural molecule having anti-proliferative, anti-inflammatory and anti-oxidant properties by inhibiting farnesyltransferase enzyme which further down regulates the NF-κB and STAT3 via Ras/Raf/MAPK pathway. Hence, in the current study we aimed to investigate the effect of POH on IMQ induced psoriatic like skin inflammation model in Balb/C mice. It was found that POH (200 mg/kg, topical application) has reduced the epidermal hyperplasia, psoriasis area and severity index (PASI) scoring; splenomegaly. Further, POH treatment has decreased the pro-inflammatory serum cytokine levels such as IL-6, IL-12/23, TNF-α and IL-1β and also reduced the expression levels of various inflammatory proteins, COX-2, iNOS, IL-17A, IL-22, NF-κB and STAT3 evidenced by Immunoblotting from skin samples. The levels of endogenous antioxidants like GSH, SOD, and Nrf2 were restored to normal levels upon POH treatment. POH downregulated the proteins levels of TLR7, TLR8, CyclinD1 and mRNA expression of Bcl-2 in the mice. POH has ameliorated the hyper-keratosis and acanthosis which was evidenced by histopathology. Immuno-fluorescence data revealed that POH has decreased the levels of Ki67, NF-κB-p-65 and STAT3 levels in skin tissues. Collectively, our results suggest that POH has a promising therapeutic application for ameliorating psoriasis-like skin inflammation.

Psoriasis is a reversible chronic auto-immune disease marked by keratinocyte hyperproliferation, epidermis, and parakeratosis. Psoriasis is not gender-specific, and it can affect both men and women at any age, however it is most common in adults. Every year, psoriasis affects 2-4 percent of the population. Psoriasis, for example, has a role in the development of various disorders. Reactive oxygen species (ROS) have the potential to harm cell components. The antioxidant system protects the body from ROS; a malfunction of the antioxidant system is implicated, as is an increase in ROS production. Inflammatory cytokines released by immune cells, such as IL-1, IL-6, TNF65, IL-12, IL-17A, IL-22, and IL-23, contribute to keratinocyte proliferation. The interleukin IL-23/IL-17 axis plays a crucial role in the pathogenesis of psoriasis, according to the aetiology of psoriasis. IL-17 has a key function in the generation of inflammatory cells, which helps to maintain the psoriasis pathophysiology [3]. Some biologics licenced for psoriatic arthritis include infliximab, adalimumab, and secukinumab, with the former two acting as TNF- or its receptor inhibitors and the latter acting as an IL-17A inhibitor with limitations. Topical therapy, phototherapy, and systemic therapy are all used to treat psoriasis. These medications include corticosteroids, vitamin D analogues, and retinoids, among others. Methotrexate, tacrolimus, and cyclosporin are some of the most commonly used medications for psoriasis. However, its long-term use is restricted due to unpleasant side effects such as myelosuppression, gastrointestinal disturbances, and hepatotoxicity. This highlights the need for an effective, safe, and effective psoriasis treatment.

Numerous natural plants have been extensively employed for various ailments, particularly those connected to inflammation, from the eras of historic medicine. Recent advanced study has also selected a path towards natural substances when considering this as a theme. Since synthesised medications with no side effects appear to be a once-in-a-blue-moon occurrence. There are numerous difficulties to be resolved, among which are high toxicity, recurrence, and inadequate rehabilitation. To address these issues, natural products such as essential oils and volatile aromatic liquids with significant physiological properties came to the fore. One of the products in this group is perillyl alcohol. POH is an essential oil that may be extracted from a variety of plants, including citrus peel, cherries, and mint. POH is a hydroxylated monoterpene structure derived from the mevalonate pathway. POH has been shown to reduce inflammation during carcinogenesis and promote apoptosis in cancer cells in a variety of malignancies, including rat mammary, liver, colon, and prostate cancers. Similarly, excessive formation of reactive oxygen species (ROS) is one of the reasons of periodontitis caused by Porphyromonas gingivalis, and perillyl alpha inhibits Fusobacterium nucleatum. POH also increased the amounts of Bcl-2, an anti-apoptotic factor that promotes apoptosis.

the opposing viewpoint POH is a farnesyltransferase inhibitor that inhibits the synthesis of T-cell cytokines at the post-transcriptional phase. Recent research has shown that Farnesyltransferase inhibitors suppress IMQ-induced psoriasis, implying that Farnesyltransferase is involved in the activation of the Ras/Raf/MEK/ERK pathways, which leads to the activation of inflammatory gene expression via NF-B-mediated upregulation of pro100 inflammatory cytok. Inhibitors of Farnesyltransferase also suppress STAT3 phosphorylation. STAT3 has a critical role in the development and pathophysiology of psoriasis and psoriatic-like inflammatory diseases as a fundamental regulator of inflammatory and immunological responses. Because of its anti-oxidant, anti-inflammatory, and apoptotic properties, we looked into the effect of POH in imiquimod-induced psoriasis.

Topical administration of imiquimod to the shaved dorsal area of mice created a psoriasis-like skin inflammation mouse model. Topical imiquimod treatment for 7 days resulted in scaling, epidermal thickness, erythema, and inflammatory infiltrates in migrating mice.

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