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Mitigative effects of a topically-applied combination of cimifugin and vinpocetine on a murine psoriasis-like model

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ABSTRACT

The chromones found in the dried roots of *Saposhnikovia divaricata* include cimifugin; in fact, *Saposhnikovia divaricata* is a main source of cimifugin. Vinpocetine is a synthetic version of vincamine derived from periwinkle; it is characterized by potent anti-inflammatory properties that allow it to reduce immune cell infiltration and suppress the release of pro-inflammatory cytokines. The objective of this study was to investigate the potential influence of a topically-applied combination of cimifugin and vinpocetine gels on a model of a psoriasis-like inflammatory skin reaction. To this end, we divided 48 albino BALB/c mice into six groups. All groups except for the negative control group received imiquimod topically (daily, for 7 days) for the induction of psoriasis-like skin lesions. A group received imiquimod (5%) only (positive control), while four other groups were also treated with a clobetasol (0.05%) cream, a cimifugin (3%) gel, a vinpocetine (3%) gel, or a combination of cimifugin (3%) and vinpocetine (3%) gels, once daily, for 7 days; the aforementioned treatments were first applied 7 days after the pharmacological induction of the lesions. Our findings revealed that the topically-applied combination of cimifugin- and vinpocetine-containing gels had an important anti-psoriatic effect, as seen by the diminishing of the skin levels of tumour necrosis factor-alpha, interleukin-17, and interleukin-23, thereby improving the imiquimod-induced histological changes in

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mice. We conclude that a topically-applied combination of cimifugin and vinpocetine can exert substantial anti-psoriatic activity.

1. Introduction

Psoriasis is a common, chronic skin disorder passed on through genetics. It is an illness that is proliferative and inflammatory. There is no known cause of psoriasis. Clinically speaking, there are five main types of psoriasis: guttate, plaque, inverse, pustular, and erythrodermic. In addition, interleukin (IL)-17 (IL-17), tumour necrosis factor-alpha (TNF-α), and interferon are known to promote keratinocyte development. Moreover, the TNF-α/Th17/IL-23 pathway is a key component of the inflammatory signalling pathway that promotes psoriasis[1].

Saposhnikovia divaricata's roots contain chromones, including cimifugin, which are essential for treating inflammatory diseases. Cimifugin has anti-inflammatory, antiproliferative, and immunoregulatory properties[2]. Vinpocetine is a synthetic version of vincamine, an alkaloid derived from the leaves of the periwinkle plant *Vinca minor*, which belongs to the Apocynaceae family; it has vasodilating and anti-inflammatory effects. Vinpocetine also has immunomodulatory and antioxidant properties, and it is marketed as a nutritional supplement for the improvement of cognition and memory. Finally, imiquimod rapidly prompts psoriasis-like inflammatory skin reactions in rodents that are similar to human psoriasis, by strongly relying on the IL-23/IL-17 axis. This quick and easy model can be used in order to assess novel therapeutic strategies and drugs[3]. This study sought to ascertain the beneficial effects of cimifugin and vinpocetine gels when used alone and in combination on the imiquimod-induced model of psoriasis in mice, through their effects on the skin levels of TNF-α, IL-17, and IL-23.

2. Methodology

2.1. Drugs and reagents

Meda AB (Sweden) is the producer of imiquimod. Cimifugin and vinpocetine were provided by HyperChem (China), while the clobetasol (0.05%) cream was obtained from GSK plc (UK).

2.2. Cimifugin and vinpocetine gel preparation

Carbopol 940 (1%) and an appropriate volume of distilled water were combined in order to create the gel, which was then thoroughly stirred. Cimifugin (or vinpocetine) was dissolved in ethanol (96%) and was sonicated so as to produce a solution. As this solution was gradually added, the Carbopol 940 dispersion was continuously agitated. While being continually mixed, triethanolamine was gradually incorporated into the mix (up to 1%). The gel's final volume was up to 50 g after adding the distilled water and agitating in order to make a homogeneous gel.

2.3. Experimental design

The work was done at the Al-Nahrain University between February 2024 and June 2024. The institution's reviewing board at the Al-Mustaqbal University College of Pharmacy has surveyed the comprehensive research plan and has licensed the hereby presented experiments. The study was conducted following the ethical principles outlined in the Declaration of Helsinki, while a local ethical board has reviewed and approved the research protocol (approval protocol number: 1025; date: 4/11/2024).

In total, 48 albino BALB/c mice with an average body weight of 28–40 g and an age of 8–12 weeks were used. The shaving of the backs of the mice took place before applying 62.5 mg of imiquimod daily to their skin. The mice were then randomly assigned into the following six groups (n=8 per group): (i) group I (negative control group; healthy mice without any treatment), (ii) group II (imiquimod 5%; mice that received 62.5 mg of the imiquimod 5% cream on the shaved dorsal skin, daily, for 7 days; induction of psoriasis-like lesions),

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(iii) group III (imiquimod 5% > clobetasol 0.05%; mice that, after the induction of the psoriasis-like lesions, have been treated with a clobetasol 0.05% cream, daily, for 7 days), (iv) group IV (imiquimod 5% > cimifugin 3%; mice that, after the induction of the psoriasis-like lesions, have been treated with a cimifugin 3% gel, daily, for 7 days), (v) group V (imiquimod 5% > vinpocetine 3%; mice that, after the induction of the psoriasis-like lesions, have been treated with a vinpocetine 3% gel, daily, for 7 days), and (vi) group VI (imiquimod 5% > cimifugin 3% + vinpocetine 3%; mice that, after the induction of the psoriasis-like lesions, have been treated with a combination of cimifugin 3% and vinpocetine 3% gels, daily, for 7 days).

2.4. Animal sacrifice and sampling

All mice were sacrificed on day 14 of the experiment by diethyl ether inhalation. Skin tissue samples were obtained and homogenized; the supernatants were stored in Eppendorf tubes (at -80°C) for the undertaking of ELISA assessments. Other skin tissue samples were also placed under a 10% formalin preservation process for the undertaking of histological assessments[4].

2.5. Measurement of IL-17, TNF-α, and IL-23 levels in skin tissue homogenates

An ELISA kit was used in order to estimate the skin levels of TNF-α, IL-17, and IL-23 according to the producer's instructions.

2.6. Statistical analysis

Data enrolled in this study were analysed using the SPSS v. 16 software. Comparison of mean levels among the study groups was done by using one-way ANOVA. The level of significance was set at $p<0.05$.

3. Results and Discussion

The application of imiquimod on the shaved murine skin (group II) produced substantial histopathological alterations, characterized by Munro abscesses, hyperkeratosis, parakeratosis, acanthosis, abnormal thickness of the epidermis, the presence of rete ridges, and marked lymphocyte infiltration and papillary congestion (results not shown). On the other hand, the histological features of the skin samples obtained from the mice treated with the combination of cimifugin and vinpocetine gels (group VI) are characterized by the absence of Munro abscesses, the absence of hyperkeratosis, the absence of parakeratosis, acanthosis, the absence of rete ridges, mild lymphocyte infiltration, and the absence of papillary congestion; similarly to the negative control group (group I; results not shown).

Table 1 provides an overview of the skin levels of TNF-α, IL-17, and IL-23 among the experimental groups of the study. In the present study, the induction of psoriasis-like skin lesions resulted in raising the skin levels of TNF-α; these levels were reduced following treatment. The best results were associated with the use of a combination of cimifugin and vinpocetine gels (group VI), while the best monotherapy results were associated with the use of the cimifugin gel (Table 1). Our results are in agreement with those of Liu *et al.*[5], since we have demonstrated the ability of cimifugin in reducing the levels of TNF-α. However, the point of originality in our study is found in the fact that we have shown that the application of a combination of cimifugin and vinpocetine gels can be associated with an even more intense reduction of the skin TNF-α levels.

In this study, the administration of imiquimod has resulted in a rise in the skin levels of IL-17 and IL-23, while the treatments have resulted in the reduction of these biomarkers' levels (Table 1). The combined treatment has again resulted in a better reduction in the skin IL-17 and IL-23 levels than the single agents. According to Liu *et al.*[5], cimifugin can efficiently invert the imiquimod-induced up-regulation of proinflammatory cytokines (including TNF-α, IL-6, IL-17A, IL-1β, and IL-22); therefore, our study results are in line with regard to the effect of cimifugin on IL-17 levels. It is also noteworthy mentioning that vinpocetine has been suggested to be able to prevent the occurrence of COVID-19, as it potentially exerts anti-inflammatory and antioxidant properties through the amelioration of the MAPK/NF-κB transcription factor pathway[6]. On the other hand, the topical administration of imiquimod to

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Table 1. Comparison of the skin tumour necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23) levels (in pg/g) among the experimental groups of the study (n=8 mice per group). Different letters (as superscripts) are used in order to express statistically-significant differences among the biomarker levels of the studied groups within each column.

Treatments / study groups (n=8 mice per group)	**TNF-α levels** (pg/g)	**IL-17 levels** (pg/g)	**IL-23 levels** (pg/g)
negative control / I	146.27 ± 9.85 ^{c}	198.70 ± 13.90 ^{b}	190.88 ± 38.65 ^{b}
imiquimod 5% (induction of psoriasis) / II	372.41 ± 52.72 ^{a}	457.79 ± 84.78 ^{a}	496.61 ± 37.71 ^{a}
imiquimod 5% > clobetasol 0.05% / III	218.72 ± 33.97 ^{b}	246.02 ± 12.62 ^{b}	161.61 ± 37.71 ^{b}
imiquimod 5% > cimifugin 3% / IV	158.96 ± 13.04 ^{b}	268.98 ± 35.60 ^{b}	248.64 ± 34.80 ^{b}
imiquimod 5% > vinpocetine 3% / V	168.86 ± 14.09 ^{b}	258.78 ± 33.50 ^{b}	263.52 ± 32.30 ^{b}
imiquimod 5% > cimifugin 3% + vinpocetine 3% / VI	116.35 ± 56.66 ^{c}	222.58 ± 24.11 ^{b}	154.64 ± 18.24 ^{b}
***p*-value** (one-way ANOVA)	<0.001	<0.001	<0.001

laboratory animals is known to not only produce cutaneous inflammatory reactions, but to also produce an excess of inflammatory mediators[7].

In our experiments, imiquimod was found to up-regulate the release of inflammatory mediators, but vinpocetine suppressed their levels. Nevertheless, as compared to the imiquimod group (group II), the administration of the vinpocetine 3% gel significantly reduced the skin levels of inflammatory cytokines such as IL-17 and IL-23 (Table 1). Al-Kuraishy *et al.*[8] have suggested that vinpocetine can reduce inflammation by suppressing the NF-κB signalling pathway and the release of pro-inflammatory cytokines (such as IL-1β, IL-6, IL-8, IL-12, and TNF-α). Since vinpocetine can inhibit the NF-κB activation in order to produce its anti-inflammatory action, it could be a promising adjunctive and a valuable drug in the treatment of inflammatory and immune-mediated diseases[9]. Finally, our experimental data regarding the skin levels of IL-17 and IL-23 suggest that vinpocetine could act as an anti-psoriatic agent. The pathogenesis of psoriasis includes IL-23; a cytokine believed to have a role in the production of IL-17 and IL-22 by the Th17 cells[10].

4. Conclusion

A topically-applied combination of cimifugin (3%) and vinpocetine (3%) gels exerts a restorative effect on the histopathological (psoriasis-like) changes induced by the application of imiquimod (5%) on the murine skin. This anti-psoriatic activity could be mediated by the anti-inflammatory and immunomodulating properties of these compounds, as evidenced in our study by the effects that they had on the skin levels of TNF-α, IL-17, and IL-23.

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Conflicts of interest

None exist.

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