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ORIGINAL ARTICLE

Autophagy-mediated regulation of psoriasis biomarkers by Dead Sea and magnetized saline waters: An *in vitro* study.

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Key words: **Dead Sea water; magnetized water; keratinocytes; psoriasis; calcitonin gene-related peptide; secreted frizzled-related protein; autophagy**

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Abstract

BACKGROUND: Dysregulated autophagy is linked to abnormal keratinocyte differentiation and persistent psoriatic inflammation. Smart fluids, such as Dead Sea Water (DSW) and saline magnetized water (MW), have emerged as potential non-pharmacological autophagy activators. This study evaluates their effects on psoriasis-like keratinocytes, focusing on calcitonin gene-related peptide (CGRP), a neuropeptide involved in pruritus and inflammation, and secreted frizzled-related protein 4 (SFRP4), whose reduced expression contributes to epidermal hyperplasia. The role of autophagy in mediating these effects was also investigated.
METHODS: Polycytokine-stimulated HaCaT keratinocytes were treated with DSW or saline MW. CGRP and SFRP4 expression levels were assessed alongside autophagy markers beclin-1 and LC3B. The involvement of autophagy was confirmed using wortmannin, an autophagy inhibitor.
RESULTS: Both DSW (4.7 ± 1.9 a.u.) and saline MW (3.6 ± 1.6 a.u.) significantly reduced CGRP expression compared to controls (non-magnetized saline: 7.5 ± 2.3 a.u.; distilled water: 7.6 ± 2.5 a.u.; all $p < 0.001$). While both fluids enhanced SFRP4 expression equally ($p = 0.78$), saline MW showed superior CGRP inhibition ($p < 0.001$). Both fluids mitigated polycytokine-induced reductions in beclin-1 and LC3B levels (all $p < 0.001$), with saline MW showing more pronounced effects ($p < 0.05$). Wortmannin impaired the effects of both fluids on CGRP and SFRP4, indicating autophagy mediation.
CONCLUSIONS: DSW and saline MW show promise as sustainable active ingredients for topical formulations targeting psoriatic inflammation via autophagy activation.

Abbreviations:

a.u.	- arbitrary units
CGRP	- calcitonin gene-related peptide
DSW	- Dead Sea water
DW	- distilled water
ELISA	- enzyme-linked immunosorbent assay
IL	- interleukin
LC3B	- microtubule-associated protein 1 light chain 3 beta
MF	- magnetic field
MW	- magnetized water
OSM	- oncostatin M
SFRP4	- secreted frizzled-related protein 4
TNF-α	- tumor necrosis factor alpha

INTRODUCTION

Psoriasis represents a complex chronic immune-mediated dermatological condition characterized by keratinocyte hyperproliferation, aberrant cellular differentiation, and persistent inflammation (Raharja *et al.* 2021). Within the intricate pathophysiology of this disorder, multiple molecular mediators demonstrate marked dysregulation, particularly in their governance of inflammatory cascades (Man *et al.* 2023) and epidermal homeostasis (Honma & Nozaki, 2021). Among these critical molecular players, calcitonin gene-related peptide (CGRP) exhibits notably heightened expression within psoriatic lesions, manifesting as increased density of CGRP-positive nerve fibers in the epidermis (Chan *et al.* 1997; Granstein *et al.* 2015). This potent vasoactive neuropeptide demonstrates dual functionality through direct stimulation of keratinocyte proliferation (Pepin *et al.* 2024) and autocrine signaling mechanisms, thereby establishing a self-perpetuating amplification cascade that promotes disease progression (Hou *et al.* 2011). Concurrent with CGRP elevation, secreted frizzled-related protein 4 (SFRP4), a crucial negative regulator of Wnt signaling, exhibits marked downregulation in lesional skin (Bai *et al.* 2015). This diminished expression contributes to pathological keratinocyte proliferation and inflammatory processes, while experimental evidence demonstrates that therapeutic restoration of SFRP4 levels attenuates psoriasiform manifestations *in vivo* (Bai *et al.* 2015). Furthermore, emerging evidence highlights the fundamental role of autophagy, a cellular recycling mechanism essential for physiological epidermal differentiation, in the pathogenesis of psoriasis (Bai *et al.* 2024; Wu *et al.* 2024). In properly differentiated keratinocytes, constitutive autophagic activity maintains homeostasis (Koenig *et al.* 2020). Notably, the interplay between CGRP and SFRP4 may modulate the autophagic flux through the mTORC1 pathway, wherein CGRP functions as an autophagic suppressor (Machado *et al.* 2019), while SFRP4 promotes autophagic activity through inhibition of this signaling cascade (Bérubé *et al.* 2024).

Recent research has underscored the potential of non-pharmacological activators of autophagy, such as Dead Sea water (DSW) and saline magnetized water (MW), in promoting skin health and homeostasis. DSW, a natural smart fluid with a distinctive mineral composition, has been extensively studied in dermatology for its anti-inflammatory and barrier-repair properties (Dai *et al.* 2023; Yan *et al.* 2024). Notably, DSW has been shown to activate autophagy-related molecular pathways in human dermal cells and reconstructed skin models (Yan *et al.* 2024). Similarly, MW, characterized by altered biophysical properties due to magnetic exposure (Lindinger 2021), has demonstrated autophagy-activating effects through topical application in clinical cohorts (García Martín *et al.* 2023; Minoretti *et al.* 2023). Building on these foundations, we designed the present study to explore the ability of DSW and saline MW to modulate the expression of CGRP and SFRP4 – two critical mediators implicated in the pathogenesis of psoriasis. This exploration was conducted using a validated *in vitro* model that leverages polycytokine-stimulated human keratinocytes (Kim *et al.* 2022). Additionally, we investigated the role of autophagy as a potential mechanism underlying these effects. The overarching aim of our research was to identify novel therapeutic strategies that harness the properties of smart fluids to target the molecular dysregulations driving psoriasis.

MATERIALS AND METHODS

Materials

Two smart fluids (DSW and saline MW) and two control fluids (saline non-MW and distilled water) were utilized in all experiments. DSW (BIO-ROM s.r.o., Bratislava, Slovakia) was procured from an online retailer. Saline MW was sourced from Aquavis srl (Brescia, Italy). The production process involved the preparation of a patented saline water solution – containing 0.9% NaCl, 0.011% KCl_2 0.009% $CaCl_2$, 0.007% $MgCl_2$, 0.007% $ZnCl_2$ and 0.007% $AlCl_2$ – which was subsequently exposed to a magnetic field (MF) of a fixed strength (3000 Gauss) for 2 h. The resulting saline MW was stored at room temperature and used within three months of preparation. For control purposes, a batch of saline water with identical salt concentrations but not exposed to a MF was used. Molecular biology-grade distilled water (DW; Sigma, St. Louis, MO, USA) served as an additional control fluid.

Experimental protocol

A visual outline of the experimental procedures is provided in Figure 1. Human immortalized keratinocytes (HaCaT cells) were obtained from CLS Cell Lines Service GmbH (Eppelheim, Germany) and cultured in Dulbecco's modified Eagle's medium (DMEM; Sigma) supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin under standard cell culture conditions (37 °C, 5% CO_2 in a humidified incubator). The cells were grown until they reached 80%

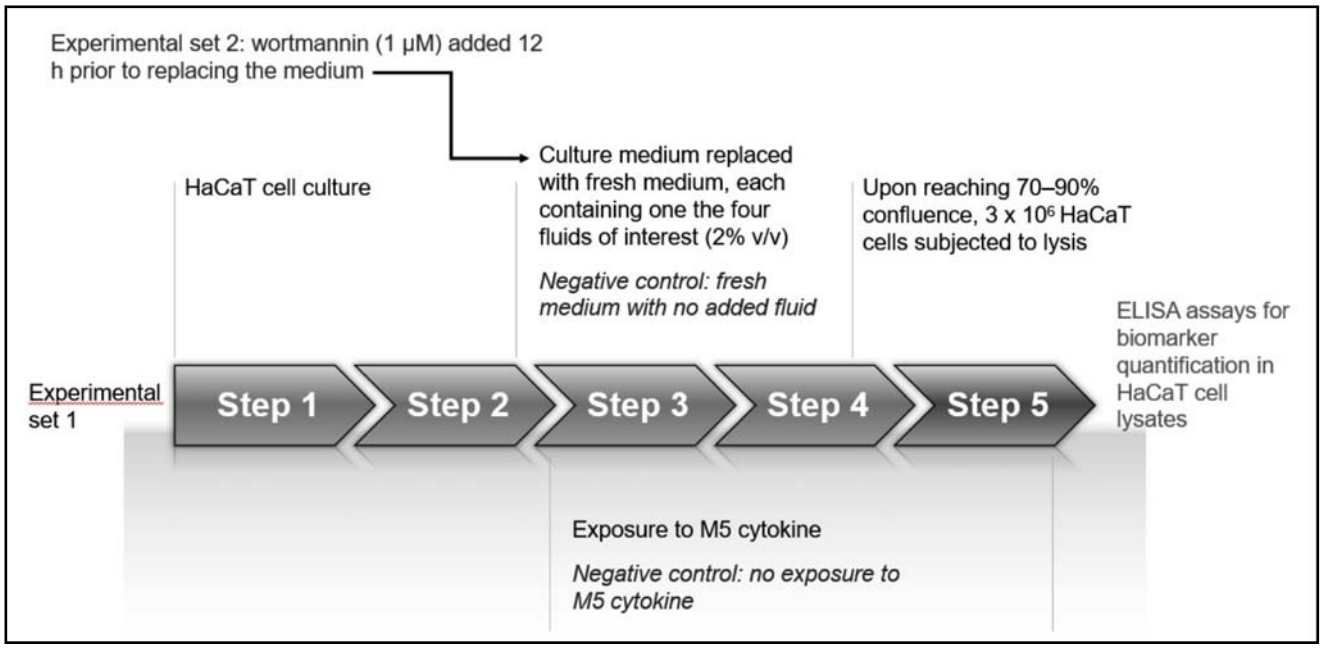

Fig. 1. Schematic representation of the experimental protocol

confluence. Two sets of experiments were designed. In the first round, 24 hours prior to UVB irradiation, the medium was replaced with fresh medium containing one of the following fluids: 1) DSW at a concentration of 2% v/v, 2) saline MW at 2% v/v, 3) saline non-MW at 2% v/v, or 4) DW at 2% v/v. The cells were subsequently exposed to a mixture of five pro-inflammatory cytokines (10 ng/mL each), namely, TNF-α, IL-17A, IL-22, IL-1, and oncostatin-M (OSM; Prospec, East Brunswick, NJ, USA) – designated as M5 cytokines – to induce a psoriasis-like cell phenotype, as previously described (Kim *et al.* 2022). Cells that neither underwent fluid pretreatment nor were exposed to M5 cytokines were used as negative controls. In the second set of experiments, to investigate whether autophagy activation induced in HaCaT cells by smart fluids could play a role in modulating CGRP and SFRP4 levels, all procedures were repeated under the same conditions but with the addition of the autophagy inhibitor wortmannin (1 μM; Sigma) (Blommaart *et al.* 1997) 12 h prior to replacing the culture medium with fresh medium (Figure 1).

Biomarker quantification in HaCaT cell lysates

Upon reaching 70–90% confluence, HaCaT culture samples (~ 3×10^6 cells) exposed to M5 cytokines underwent lysis in an appropriate buffer (200 μL), followed by a 10-min centrifugation at 13000 × g. CGRP (Abnova, Taipei City, Taiwan) and SFRP4 (MyBioSource Inc., San Diego, CA, USA) concentrations in HaCaT cell lysates were measured using commercially available ELISA kits according to the manufacturers' protocol. All biomarker measurements are expressed in arbitrary units (a.u.), with reference values set at 1 for cells that did not receive fluid pretreatment and were not exposed to M5 cytokines.

Data analysis

Continuous data are presented as the mean ± standard deviation (SD) of at least three independent experiments, each conducted in duplicate. To compare the different experimental conditions, an unpaired one-way analysis of variance (ANOVA) was performed, followed by Tukey's *post hoc* test to identify significant differences between groups. Analyses were carried out using SPSS, version 20.0 (IBM, Armonk, NY, USA), and two-tailed p values < 0.05 were considered statistically significant.

RESULTS

Smart fluids reduce CGRP and promote SFRP4 expression in stimulated HaCaT cells

Following stimulation with M5 cytokines, cell lysates from HaCaT cells exposed to DW (7.6 ± 2.5 a.u.) and saline non-MW (7.5 ± 2.3 a.u.) exhibited significantly elevated levels of CGRP compared to unstimulated control cells not exposed to any fluid (Table 1). The increase observed with the two control fluids was similar. Notably, pre-treatment with DSW (4.7 ± 1.9 a.u.) and saline MW (3.6 ± 1.6 a.u.) significantly reduced CGRP expression in polycytokine-stimulated keratinocytes (all $p < 0.001$) relative to two control fluids, with saline MW demonstrated superior efficacy compared to DSW ($p < 0.001$). Compared to unstimulated control cells not exposed to any fluid, stimulation with M5 cytokines significantly reduced SFRP4 expression in HaCaT cells exposed to the two control fluids (saline non-MW: 0.72 ± 0.12 a.u.; distilled water: 0.70 ± 0.16 a.u.; all

Tab. 1. CGRP and SFRP4 levels in polycytokine-stimulated HaCaT cells exposed to different experimental conditions

	Negative control	Distilled water	Saline non-magnetized water	Dead Sea water	Saline magnetized water
M5 cytokine stimulation	No	Yes	Yes	Yes	Yes
CGRP, a.u.	1	7.6 ± 2.5	7.5 ± 2.3	4.7 ± 1.9*	3.6 ± 1.6*,†
SFRP4, a.u.	1	0.70 ± 0.16	0.72 ± 0.12	0.93 ± 0.15*	0.91 ± 0.17*

Abbreviations: CGRP, calcitonin gene-related peptide; SFRP4, secreted frizzled-related protein 4. Data are means ± standard deviation of at least three independent experiments. The negative control cells were conventionally set at 1. *p < 0.001 *versus* distilled water and saline-non magnetized water; †p < 0.001 *versus* Dead Sea water.

Tab. 2. Levels of autophagy biomarkers in polycytokine-stimulated HaCaT cells exposed to different experimental conditions

	Negative control	Distilled water	Saline non-magnetized water	Dead Sea water	Saline magnetized water
M5 cytokine stimulation	No	Yes	Yes	Yes	Yes
Beclin-1, a.u.	1	0.65 ± 0.11	0.66 ± 0.14	0.81 ± 0.16*	0.92 ± 0.18*,†
LC3B, a.u.	1	0.68 ± 0.14	0.64 ± 0.17	0.85 ± 0.19*	0.94 ± 0.21*,†

Data are means ± standard deviation of at least three independent experiments. The negative control cells were conventionally set at 1. *p < 0.001 versus distilled water and saline-non magnetized water; †p < 0.05 versus Dead Sea water.

p < 0.001). Both DSW (0.93 ± 0.15 a.u.) and saline MW (0.91 ± 0.17 a.u.) were significantly effective in preventing polycytokine-induced SFRP4 down-regulation compared to the two control fluids (both p < 0.001), without significant differences among each other (p = 0.78)

Smart fluids attenuate autophagy inhibition in stimulated HaCaT cells

We subsequently investigated the levels of two autophagy biomarkers – beclin-1 and LC3B – in HaCaT cell lysates under different experimental conditions (Table 2). Expectedly, following exposure to M5 cytokines, cells exposed to DW showed significant reductions in both beclin-1 (0.65 ± 0.11 a.u.) and LC3B (0.68 ± 0.14 a.u.) levels compared to unstimulated keratinocytes (both p < 0.001). Similar decreases were observed in cells treated with saline non-MW (beclin-1: 0.66 ± 0.14 a.u.; LC3B: 0.64 ± 0.17 a.u., both p < 0.001), with no significant differences between the two control fluids (p = 0.79). However, pretreatment with the two smart fluids significantly attenuated polycytokine-induced autophagy inhibition. Specifically, DSW maintained higher levels of both beclin-1 (0.81 ± 0.16 a.u.) and LC3B (0.85 ± 0.19 a.u.) compared to both control fluids (all p < 0.001). Notably, saline MW demonstrated significantly greater autophagy-preserving effects, maintaining near-normal levels of both beclin-1 (0.92 ± 0.18 a.u.) and LC3B (0.94 ± 0.21 a.u.), which were significantly higher than those observed with DSW (both p < 0.05).

Tab. 3. Levels of autophagy biomarkers, CGRP, and SFRP4 in HaCaT cells pretreated with wortmannin and exposed to different experimental conditions

	Negative control	Distilled water	Saline non-magnetized water	Dead Sea water	Saline magnetized water
M5 cytokine stimulation	No	Yes	Yes	Yes	Yes
Beclin-1, a.u.	1	0.26 ± 0.09	0.27 ± 0.11	0.25 ± 0.12	0.24± 0.14
LC3B, a.u.	1	0.29 ± 0.12	0.30 ± 0.13	0.31 ± 0.11	0.28 ± 0.12
CGRP, a.u.	1	10.2 ± 3.7	10.4 ± 3.9	8.7 ± 2.6*	8.3 ± 2.9*
SFRP4, a.u.	1	0.44 ± 0.12	0.46 ± 0.14	0.50 ± 0.11	0.49 ± 0.12

Abbreviations: CGRP, calcitonin gene-related peptide; SFRP4, secreted frizzled-related protein 4. Data are means ± standard deviation of at least three independent experiments. The negative control cells were conventionally set at 1. *p < 0.05 versus distilled water and saline-non magnetized water.

Pharmacological inhibition of autophagy markedly impairs the protective effects of smart fluids in cultured keratinocytes

As expected, pretreatment of HaCaT cells with the autophagy inhibitor wortmannin significantly suppressed the expression of beclin-1 and LC3B across all experimental conditions (Table 3). In addition, wortmannin significantly exacerbated polycytokine-induced increase in CGRP and decrease in SFRP4 HaCaT cells compared to experiments conducted without its addition (Table 1, all $p < 0.001$). Notably, wortmannin substantially impaired the protective effects of both DSW and saline MW against polycytokine-induced increase in CGRP, although both smart fluids retained a slight protective effect when compared to the two control fluids (both $p < 0.05$). Conversely, the preventive effect against SFRP4 was completely abrogated.

DISCUSSION

In this investigation, we assessed the potential of two eco-compatible smart fluids, DSW and saline MW, using an established *in vitro* model to evaluate their effects on molecular mediators involved in psoriatic pathophysiology in polycytokine-challenged keratinocytes (Kim *et al.* 2022). Our analysis specifically targeted CRGP, a neuropeptide that, when upregulated, contributes to pruritus and psoriatic inflammation by activating immune cells and keratinocytes (Chan *et al.* 1997; Hou *et al.* 2011; Granstein *et al.* 2015; Pepin *et al.* 2024). Additionally, we focused on SFRP4, a negative regulator of Wnt signaling whose downregulation is implicated in epidermal hyperproliferation and psoriatic plaque formation (Bai *et al.* 2015). By exploring these key biomarkers, we sought to elucidate the potential of DSW and saline MW as innovative topical agents for managing psoriasis, complementing established therapeutic strategies. Our results revealed that prophylactic exposure to both smart fluids significantly mitigated the polycytokine-induced elevation of CGRP in cellular extracts. Notably, saline MW demonstrated superior inhibitory effects compared to DSW, underscoring its enhanced potential for alleviating inflammation and pruritus in psoriatic conditions. Furthermore, both smart fluids effectively counteracted the polycytokine-mediated suppression of SFRP4 expression with comparable efficacy, suggesting their shared ability to address key molecular disruptions associated with epidermal hyperproliferation.

There is increasing evidence supporting the therapeutic benefits of DSW in psoriasis management. Dead Sea balneotherapy, which involves bathing in mineral-rich DSW, has been consistently shown to reduce inflammation, promote immunomodulation, and enhance skin barrier function (Emmanuel *et al.* 2020; Harari 2024). Traditionally, DSW has been considered effective through mechanical (e.g., exfoliation) and chemical (e.g., mineral absorption) mechanisms, leading to reduced epidermal thickness and normalization of cellular proliferation markers (Emmanuel *et al.* 2024). However, to our knowledge, no prior studies have demonstrated that DSW can directly modulate key pathophysiological markers of psoriasis, such as CGRP and SFRP4, in stimulated keratinocytes. If independently validated, our findings could broaden the scope of DSW applications, transitioning its use from primarily cosmetic purposes to complementary and alternative treatments for psoriatic skin lesions. This potential aligns with recent findings by Yan *et al.* (2024), who demonstrated that DSW can activate both anti-inflammatory and autophagy-related pathways. Notably, autophagy – a cytoplasmic degradative pathway crucial for mitigating excessive inflammation through the downregulation of inflammatory proteins and signaling pathways – plays a pivotal role in the pathogenesis of psoriasis (Kim *et al.* 2022; Bai *et al.* 2024; Wu *et al.* 2024). Building on this understanding, we hypothesized that DSW might modulate CGRP and SFRP4 levels by alleviating polycytokine-induced impairments in autophagic flux within keratinocytes. In parallel, recent studies have suggested that saline MW can also activate autophagy when applied topically to human skin (García Martín *et al.* 2023; Minoretti *et al.* 2023). To investigate this further, we evaluated the ability of the two smart fluids to mitigate the decline in autophagy-related proteins in polycytokine-exposed HaCaT cells. Our findings revealed that both fluids significantly counteracted the polycytokine-induced reduction in beclin-1 and LC3B, with saline MW demonstrating more pronounced effects. Moreover, given that saline MW also surpassed DSW in suppressing CGRP levels following the polycytokine challenge, it is plausible that the observed reduction in CGRP may be mediated through autophagy activation. This hypothesis was further reinforced by CGRP's known autophagy-inhibitory properties (Machado *et al.* 2019), which seem to be effectively counteracted by pretreatment of keratinocytes with smart fluids. Conversely, both DSW and saline MW effectively antagonized the polycytokine-induced decline in SFRP4 expression – a molecule whose downregulation not only contributes to epidermal hyperproliferation (Bai *et al.* 2015) but also independently promotes autophagic activity (Bérubé *et al.* 2024). Notably, treatment with wortmannin markedly attenuated the modulatory effects of both DSW and saline MW on the two psoriasis biomarkers, indicating that their benefits should be primarily attributable to autophagy activation in pretreated HaCaT cells. However, the precise mechanisms through which these fluids enhance autophagic flux in keratinocytes remain speculative. Hypersaline waters like DSW are known to induce ionic osmotic stress, a condition against which autophagy serves as an adaptive response (Yan *et al.* 2024). Similarly, the alkaline stress elicited by saline MW could represent another pathway leading to autophagy activation.

Interestingly, non-magnetized saline water failed to exhibit modulatory effects or activate autophagy in our study, suggesting that the increased electrical conductivity, pH values, and shear viscosity induced in water by MF treatment may play a role in activating autophagy-related pathways (Minoretti & Emanuele, 2024). Nonetheless, further research is needed to elucidate the specific molecular mechanisms underlying the ability of DSW and saline MW to promote autophagic flux and their broader implications for psoriasis management.

In conclusion, the present study demonstrates that DSW and saline MW exert significant modulatory effects on key biomarkers of psoriatic pathophysiology, including CGRP and SFRP4, through autophagy activation in polycytokine-challenged keratinocytes. These findings support the potential application of smart fluids as sustainable, non-toxic, and cost-effective topical agents for psoriasis management. However, further *in vivo* studies are essential to confirm their clinical relevance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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