

Colloidal Oatmeal (*Avena Sativa*) Improves Skin Barrier Through Multi-Therapy Activity

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ABSTRACT

Oats (*Avena sativa*) are a centuries-old topical treatment for a variety of skin barrier conditions, including dry skin, skin rashes, and eczema; however, few studies have investigated the actual mechanism of action for the skin barrier strengthening activity of colloidal oatmeal. Four extracts of colloidal oatmeal were prepared with various solvents and tested in vitro for skin barrier related gene expression and activity. Extracts of colloidal oatmeal were found to induce the expression of genes related to epidermal differentiation, tight junctions and lipid regulation in skin, and provide pH-buffering capacity. Colloidal oatmeal boosted the expression of multiple target genes related to skin barrier, and resulted in recovery of barrier damage in an in vitro model of atopic dermatitis. In addition, an investigator-blinded study was performed with 50 healthy female subjects who exhibited bilateral moderate to severe dry skin on their lower legs. Subjects were treated with a colloidal oatmeal skin protectant lotion. Clinically, the colloidal oatmeal lotion showed significant clinical improvements in skin dryness, moisturization, and barrier. Taken together, these results demonstrate that colloidal oatmeal can provide clinically effective benefits for dry and compromised skin by strengthening skin barrier.

J Drugs Dermatol. 2016;15(6):684-690.

INTRODUCTION

Oats (*Avena sativa*) have been cultivated since the Bronze Age, and the use of oats as a topical therapy for variety of dermatological conditions dates to Roman times. Initially, colloid baths were prepared by boiling oatmeal to extract the gelatinous colloidal material.[1] In the early to mid twentieth century in the recorded scientific literature the term of colloidal oatmeal was beginning to appear.[2] In 1945, a ready-to-use colloidal oatmeal became available, and soon after several clinical studies demonstrated its benefits as a remedy for inflamed, dry and itchy skin dermatoses.[3-5] In 2003, the FDA approved the use of colloidal oatmeal as a skin protectant, and currently colloidal oatmeal is commonly used for skin rashes, erythema, burns, itch, and eczema.[5,6]

Despite a rich history of traditional use, the exact mechanisms of action that give colloidal oatmeal its clinical benefits remain unknown. A recent study has reported that colloidal oatmeal can reduce the expression of pro-inflammatory mediators in keratinocytes and decrease activation of the NF-kB pathway, which could contribute to the anti-inflammatory activity of colloidal oats on irritated skin.[7] In addition, Chon and colleagues recently reported that a lipophilic extract isolated from oats can induce ceramide synthesis in keratinocytes through activation of the PPAR pathway.[8] We conducted a series of in vitro experiments and a clinical study to help identify the mechanism of action for the clinical benefit of colloidal oatmeal on skin barrier. Extracts of colloidal oatmeal were prepared using organic and aqueous solvents to concentrate constituents based on compound polarity, and were subjected to molecular and functional assays related to skin barrier. In addition, an investigator-blinded clinical study was conducted to evaluate the efficacy of a colloidal oatmeal skin protectant lotion in improving barrier function in moderate to severely dry skin. Results of these studies demonstrate that colloidal oats can increase skin's expression of epidermal differentiation targets and lipids involved in barrier function, can provide pH-buffering capacity for skin and can clinically improve skin barrier function. Thus, colloidal oatmeal as an ingredient provides a multi-therapy approach for dry and compromised skin by strengthening skin barrier.

MATERIALS AND METHODS

Preparation of Extracts of Colloidal Oatmeal

Four extracts of colloidal oatmeal were prepared using HPLC-grade hexanes, 80% aqueous acetone, 80% aqueous methanol, and water to generate extracts enriched in phytochemicals based on polarity as previously described.[7] For cell culture experiments, stock solutions of each extract were dissolved in DMSO (50 mg/mL) and diluted into media (DMSO < 0.01%).

In Vitro Skin Models and Treatment

Epidermal equivalents (EPI 200 HCF) were purchased from MatTek (Ashland, MA). Equivalents were topically treated (2mg/cm^2) with colloidal oatmeal skin protectant lotion twice every 24 hours. Equivalents were incubated for 48 hours at 37°C with maintenance medium then tissues were harvested for the protein or mRNA expression analysis. Primary human

keratinocytes (PromoCell GmbH, Heidelberg, Germany) were maintained in Keratinocyte Growth Medium-2 in the presence of supplements and 0.06mM $CaCl_2$ (PromoCell). Additional $CaCl_2$ was added to induce differentiation at the point of treatment. Keratinocytes were treated for 48 hours in the presence of 1.2 mM $CaCl_2$ with colloidal oatmeal extract or vehicle (DMSO).

Gene Expression

RNA was extracted from primary human keratinocytes or epidermal human skin equivalents using Qiagen RNeasy Plus Mini kit with DNase I digestion (Qiagen, Valencia, CA). Reverse transcription was performed using High Capacity cDNA kit (Life Technologies, Grand Island, NY). 40 to 60ng of cDNA samples were used in a qPCR reaction to measure CLDN4, CLDN7, TGM1, ELOVL4, UGCG, HMGCR, and PPARβ/δ using ABI 7500 fast amplifier. All gene expression data were normalized by reference gene, polymerase (RNA) II polypeptide A (POLR2A), and verified using GAPDH. Statistical significance ($P< 0.05$) was determined by one-way ANOVA. Gene expression is reported relative to untreated samples or vehicle control.

Protein ELISAs

Epidermal skin equivalents were homogenized on ice in RIPA buffer (Alfa Aesar, Ward Hill, MA) in the presence of protease inhibitors (Sigma, St Louis, MO). Homogenates were centrifuged at 14,000 × g at 4°C for 15 min. Total protein in was measured in supernatants by bicinchoninic acid protein assay (BCA) (Pierce Biotechnology, Rockford, IL) and ANGPTL4 immunoassay was carried out using Milliplex Map Human Liver Protein Magnetic Bead Panel hANGPTL4-MAG (EMD Millipore, Billerica, MA) according to manufacturer's instructions on a Luminex xMAP platform (Luminex Corporation, Austin, TX). ANGPTL4 concentrations were normalized per mg protein. Involucrin protein level was assessed in keratinocytes whole cell extracts using Milliplex Map Human Skin Magnetic Bead INVOL-MAG (EMD Millipore, Billerica, MA).

PH Buffering

Extracts prepared for buffering capacity determination were in the form of water insoluble solids. The solids were dispersed in water to enable pH measurements and titration with hydrochloric acid (HCl). The pH of the dispersed samples was measured before and after the titration. Hydrochloric acid solutions (0.001 to 0.01N) were used to drop the pH by one unit. The initial pH of the samples ranged between pH 5 to 9. Buffering capacity was determined and expressed as the micro equivalent of hydrogen ions required to change the pH of the sample equivalent by one pH unit using previously published procedures (28). The given formula was used for calculation of the buffering capacity (BC) value: BC (μeq H+ ions) = (Na*Va)/W, wherein: Na = Normality of acid (mol/L); Va = Volume of acid used (L); W = weight of material used (g).

Measurement of Transepithelial Electrical Resistance (TEER)

For TEER immature epidermal skin equivalents (EPI-20, Mat-Tek Corporation, Ashland, MA) were transferred to medium containing 100ng/ml IL-4, 100 ng/ml IL-13, 50ng/ml IL-31 and 30ng/ml TNFα (R&D Systems, Minneapolis, MN). Colloidal oatmeal skin protectant lotion was applied topically twice every 24 hours after 4 hours of pretreatment with cytokines. TEER was measured at 0, 24, and 48 hours by using Millicell ERS-2 Epithelial Volt-Ohm Meter (Milipore). Tissues were placed in six-well tissue culture plates containing 5ml of culture medium and overlaid with 400 ml of PBS for the time required to measure electrical resistance The percentage change in TEER between time 0 (100%) and time 24 hours was expressed as follows: (TEER24hours/TEER0hours)X100.

Clinical Study Design

A five-week investigator-blinded randomized clinical study was conducted to demonstrate the effectiveness of an oatmeal skin protectant lotion in improving the moisture and barrier function of moderate to severe dry skin and to measure the residual skin effects after treatment is stopped. A standard Kligman Regression model was utilized. The protocol was approved by an IRB and informed consent was obtained from all subjects. Following a conditioning period, subjects used the oatmeal skin protectant lotion on their lower leg twice a day for a period of three weeks (Days 1-21). For the following 2 weeks (Days 22-34), subjects did not use the test product or any other lotions on their legs. Dry skin was evaluated by an expert graded and instrumental analysis (trans-epidermal water loss and Skicon) measured barrier function and skin moisture. Statistical analysis of data was performed to determine efficacy.

Population

50 subjects completed the study. Subjects were healthy females, between the ages of 18-65 years old, with moderate to severe dry skin on both lower legs at the time of enrollment. Subjects washed with a standardized soap for five days prior to the baseline visit.

TABLE 1.

Summary of Colloidal Oat Extracts		
Extraction solvent	Abbreviation	Expected Phytochemistry
Hexanes	HCO	Oils and lipophilic compounds
80% Acetone	ACO	Mid-polar compounds
80% MeOH	MCO	Mid-polar to polar compounds
Water	WCO	Polar compounds such as proteins and carbohydrates

In Vivo Treatment

Subjects applied the colloidal oatmeal skin protectant lotion twice a day for three weeks to the lower leg area. Subjects were instructed to apply an approximate amount of the lotion from the knee to the ankle. Product applications were made at a minimum of 8 hours apart. For the following 2 weeks, no treatment or any moisturizing products were applied to the lower leg area. A mild cleanser was provided for use during all showering or bathing. No product related adverse events were observed during the study.

Measurements

Dry skin was evaluated by an expert grader and instrumental analysis (trans-epidermal water loss (TEWL): Dermalab (Cortex Technology, Denmark) and Moisture measurements: Skicon 200 EX (IBS Co, Japan)) at baseline and various time points over the 5-week study.

Statistical Analysis

The data used in the statistical analysis were the changes from baseline. For the analysis of visual dryness scores, a Wilcoxon's Signed Rank Test was conducted at each post treatment time point. A Student's t-test was used at each post treatment time point for the analysis of moisturization and transepidermal water loss data, with significance set at $P<0.05$.

RESULTS

Preparations of Extracts

The hexane extract of colloidal oatmeal (HCO) generated an oily residue (3.8% yield); the aqueous acetone extract of colloidal oatmeal (ACO) generated a sticky amorphous powder (2.6% yield); the aqueous methanol extract of colloidal oatmeal (MCO) generated a dry amorphous powder (2.5% yield); the water extract of colloidal oatmeal (WCO) generated a white powder (0.7% yield). An approximate qualitative composition of each extract based on the nature of extraction processes is presented in Table 1 along with a summary of bioactivities.

Colloidal Oatmeal Extracts Upregulated Barrier Genes

We first analyzed whether colloidal oatmeal extracts can modulate expression of key target genes associated with skin barrier in human primary keratinocytes (KCs). MCO, ACO, and HCO extracts dose-dependently induced mRNA expression

FIGURE 1. Colloidal oatmeal extracts upregulated skin barrier biomarkers in primary human keratinocytes.
(A) Effect of colloidal oatmeal extracts on mRNA level of key regulators of skin barrier. Primary human keratinocytes were cultured in 1.2 mM of CaCl2 in the presence or absence of colloidal oatmeal extracts for 48 hours. RNA was extracted from the cells and the levels of ELOVL4, TGM1, IVL and CLDN7 were evaluated by real time quantitative PCR. Data were presented as fold activation over vehicle (mean ± SEM from triplicates). (B) Involucrin protein expression level was evaluated by ELISA in whole cell KC extracts at 48 hours after treatment with 50 PPM MCO. VEH-vehicle control (DMSO). HCO, MCO, WCO and ACO – hexane, methanol, water and acetone oatmeal extracts, respectively.
* $P<0.05$, ** $P<0.01$, *** $P<0.001$ compared with VEH.

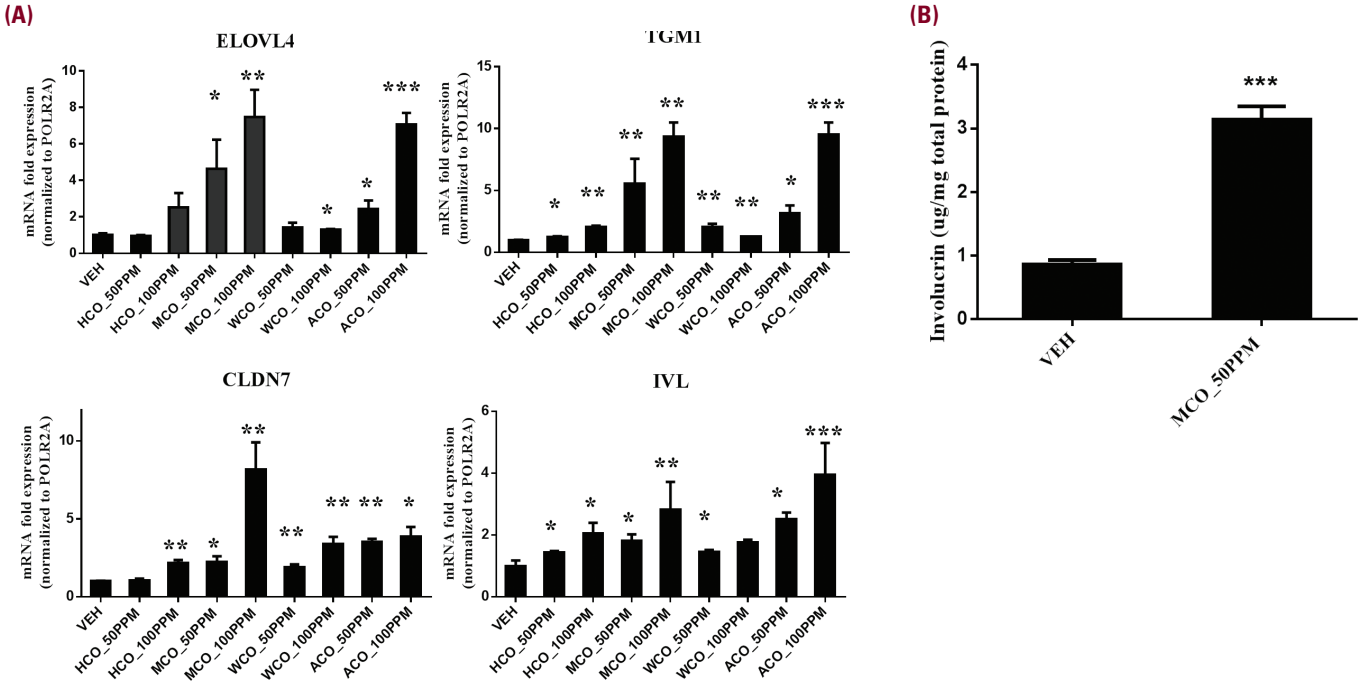


TABLE 2.

Buffering Capacity of Colloidal Oatmeal, Water Extract of Colloidal Oatmeal, and Its Fractions	
Sample	**Buffer capacity**
colloidal oat	40.8
water extract of colloidal oatmeal	142.0
>20kDa fraction	114.0
<20kDa fraction	52.6
<3kDa fraction	89.5
3-20kDa fraction	17.1

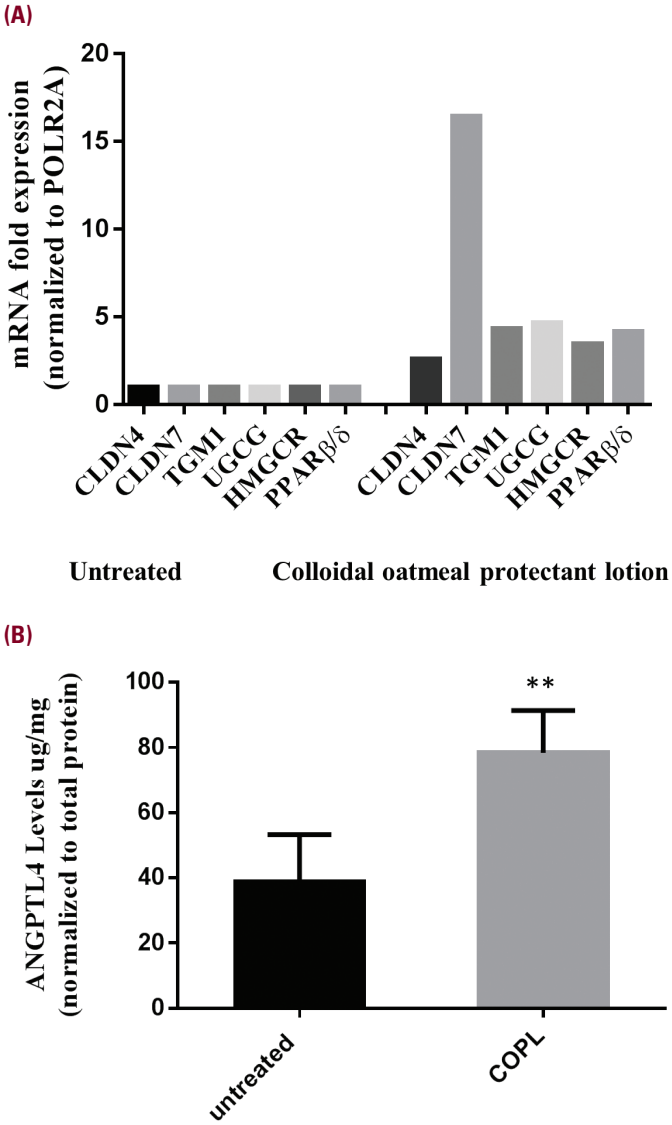
of epidermal differentiation markers involved in cornified envelope formation, transglutaminase-1 (TGM1), and involucrin (IVL) compared with vehicle control (Figure 1A). We also observed an enhancement of mRNA level of claudin-family tight junction (TJ) protein claudin-7 (CLDN7) induced by MCO and ACO. Additionally, mRNA expression of enzyme involved in the synthesis of long chain FFAs, and acyl-ceramide synthesis, elongase of very long chain fatty acids-4 (ELOVL4), was upregulated following treatment with MCO, ACO, and HCO. MCO also resulted in a 3-fold upregulation of involucrin protein levels in primary keratinocytes (Figure 1B).

Colloidal Oat Enhanced Expression of Barrier Genes

The pH buffering capacity (BC) of whole colloidal oatmeal water extract and its fractions were investigated (Table 2). The BC of the water extract of colloidal oat was significantly higher (BC=142) than the BC of the native colloidal oat (BC=40.8). The extract is enriched in globulin proteins (20-35 kDa and 50-60 kDa), assessed by protein gel electrophoresis analysis (data not shown) and consistent with previously published data,[9] and carbohydrates. The >20 kDa fraction, which contains primarily globulins, had a slightly lower BC=114 than the crude water extract. The fraction isolated in the 3-20 kDa range presumably contains the gluteins, as well as some prolamins,[9] did not significantly contribute to the overall BC of colloidal oat (Table 2). Collectively, the buffering capacity demonstrated that the water extract of colloidal oatmeal possessed effective pH buffering activity, suggesting that colloidal oats can be beneficial for skin by helping to provide a skin barrier with enhanced pH buffering capacity and therefore potentially aid in protection against irritants.

We next analyzed expression of barrier regulatory genes in human skin equivalents after topical application of colloidal oatmeal protectant lotion. The colloidal oatmeal containing lotion significantly induced the expression of TJ genes CLDN7 and CLDN4, and other target genes including TGM1, HMG-CoA reductase (HMGCR - the key enzyme of cholesterol synthesis), and ceramide glucosyltransferase UGCG (which is involved in the initial step of glycosphingolipid synthesis; Figure 2A). Furthermore, an increase in the expression of PPARβ/δ (transcription factor with critical roles in regulating lipid homeostasis) and its direct target protein ANGPLT4-encoding adipocytokine was also observed (Figure 2B). Taken together, these results demonstrate that the colloidal oatmeal up-regulated genes of key biological targets responsible for the functionality of the cellular and lipid skin barrier and therefore can provide overall skin barrier related benefits.

FIGURE 2. Colloidal oatmeal lotion upregulated skin barrier markers in human epidermal skin equivalents. Human epidermal skin equivalents were treated with topical application of colloidal oatmeal lotion for 48 hours. (A) mRNA was isolated and changes in mRNA level for CLDN4, CLDN7, TGM1, UGCG, HMGCR, and PPARβ/δ were assessed by real time quantitative PCR. Data were presented as fold activation over untreated. (B) Total protein was extracted from tissues and ANGPLT4 level was assessed by ELISA, as described in Materials and Methods. COPL-colloidal oatmeal protectant lotion.
**P<0.01 compared with untreated



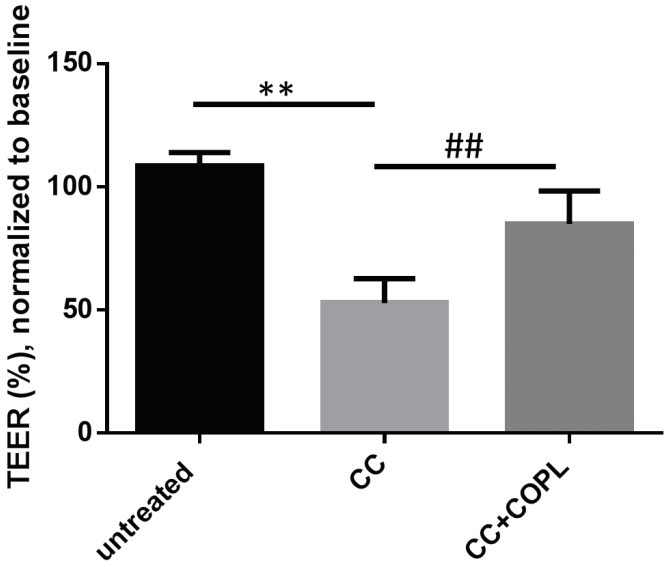
Colloidal Oatmeal Helped in the Recovery of Cytokine-induced Barrier Disruption

T-helper cell 2 (Th2)-derived cytokines Il-4, Il-13, IL-31 and pro-inflammatory TNF-α have previously been reported to down-regulate expression of key barrier genes such as fillaggrin (FLG), loricrin (LOR) and involucrin (IVL)[10,11] that leads to differentiation defects and reduced lipid envelope reminiscent of atopic dermatitis. To generate inflammatory skin phenotype and therefore weaken skin barrier we exposed developing human epidermis to a cocktail of four above mentioned cytokines. We employed a transepithelial electrical resistance TEER method to quantify the barrier integrity and evaluate TJ barrier function.[12] We found remarkable (52%) decrease in TEER at 48 hours after treatment with cytokines compared with the untreated tissues (Figure 3). This condition was significantly alleviated by topical colloidal oatmeal skin protectant lotion treatment (32% of protection compared with cytokines alone).

Colloidal Oatmeal Lotion Significantly Improved Skin Dryness, Hydration and Skin Barrier Integrity In Vivo

Clinical evaluations of skin dryness of individuals with moderate to severe dry skin showed significant improvements (P<0.05) at all time-points during the treatment and regression period with the colloidal oatmeal protectant lotion, including 13 days after the last application when compared to baseline values (Figure 4). Skin was significantly (P<0.05) more hydrated at all time periods measured during both the treatment and regression period. After 3 weeks of treatment, there was highly significant (P<0.05) increase in skin moisture when compared to the baseline mean score. At the end of the regression phase (2 weeks no treatment) mean moisturization values were still significantly higher than baseline suggesting the maintenance of barrier homeostasis. Skin barrier integrity and hydration was also assessed by transepidermal water loss (TEWL) measurements.[13] Reduced TEWL values indicated a significant improvement in skin barrier (P<0.05) at all time points during the treatment period and up to day 9 of the regression (no treatment) phase of the study.

FIGURE 3. Colloidal oatmeal lotion protected skin barrier from disruption caused by cytokines. Untreated or colloidal oatmeal protectant lotion-treated (COPL) epidermal skin equivalents were incubated in the presence or absence of cytokine cocktail (CC) containing TNF-α (30ng/mL), IL-4 (100ng/mL), IL-13 (100ng/mL) and IL-31 (50ng/mL) and TEER was measured at 48 hours.
**P<0.01 compared with untreared, ##P<0.01 compared with CC

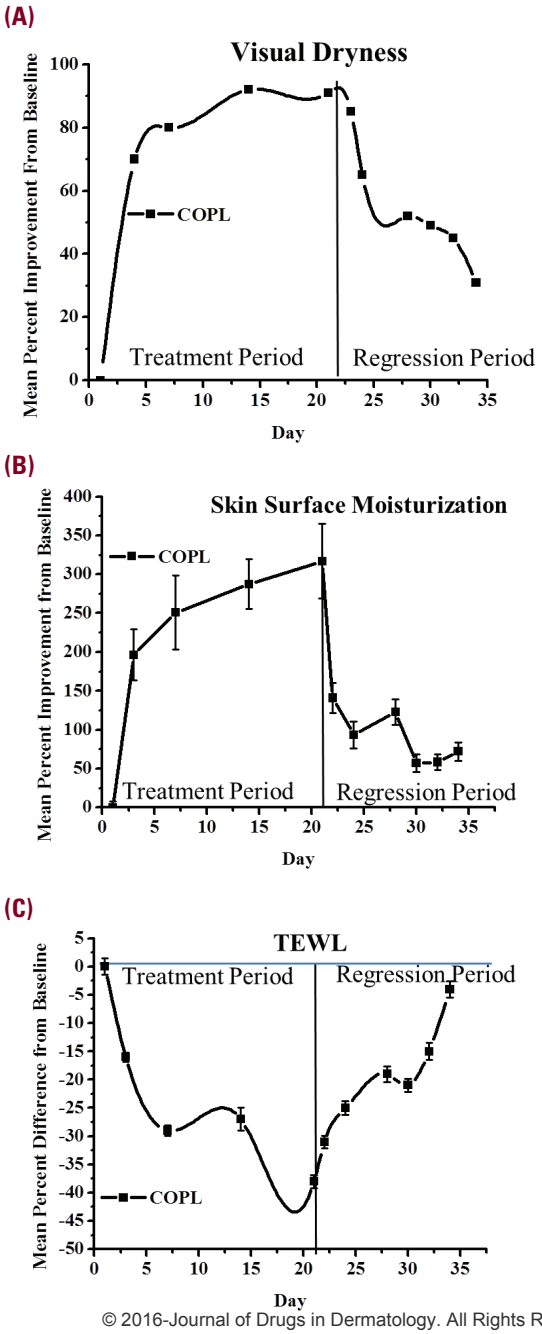


DISCUSSION

The aim of this study was to investigate the mechanism of action of colloidal oatmeal on skin barrier in vitro and in vivo. Treatment of primary human keratinocytes with colloidal oatmeal extracts significantly induced the gene expression of key skin barrier biomarkers that was accompanied by production of involucrin, a protein required for the formation of the cornified envelope (Figure 1). Our study further demonstrates that the topical application of the colloidal oatmeal lotion was able to enhance expression of genes involved in keratinocyte differentiation (TGM1), lipid production (PPARβ/δ, HMGCR and UGCG) and TJ formation (CLDN4 and CLDN7) in the human skin equivalent model (Figure 2) suggesting an enhancement in cornified cell envelope maturation, permeability barrier structure and TJ integrity, respectively, in normal skin.[14] The fractions of colloidal oat that resulted in the greatest induction of skin barrier gene expression were the methanol and acetone extracts, which contain phenolic compounds such as flavonoids and avenanthramides, and alcohol-soluble albumin proteins.

The current study determined that colloidal oatmeal protected the epidermal skin barrier from the damage caused by exogenous treatment with cytokines in epidermal skin model of atopic dermatitis. Th2 cytokine treatment in combination with TNF-α perturbs skin barrier by inhibiting differentiation of keratinocytes, inducing cytoskeletal rearrangement and disturbing TJ integrity, and mimics atopic dermatitis skin.[10,11,15] Using a skin barrier integrity test we observed a remarkable reduction of TEER following treatment with Th2 cytokines and TNF-α, and the colloidal oatmeal protectant lotion treatment significantly alleviated the damaging effect of cytokines on skin barrier (Figure 3). The inflammation reduction and barrier improvement by colloidal oatmeal can be also potentially triggered by up-regulation of the nuclear hormone receptor PPARβ/δ and its target gene, ANGPTL4. Indeed, PPARα and PPAR β/δ activators significantly inhibited Th2-mediated inflammation and decreased generation of Il1-α and TNF-α in murine model of dermatitis.[16] Evidence for the important role of PPARα, PPARβ/δ and LXR activators in regulation of normal and compromised barrier function is emerging.[8,16-19] Collectively these in vitro results suggest that the colloidal oatmeal protectant lotion could be beneficial for dry or compromised skin conditions such as xerosis or atopic dermatitis.

FIGURE 4. The effectiveness of the oatmeal lotion in improving and maintaining barrier function and moisture levels of moderate to severe dry skin. (A) Visual dryness. Expert grader evaluations showed significant improvement ($P<0.05$) in visual dryness at all time points when compared to baseline values. (B) Conductance measurements show significant increase in skin moisturization ($P<0.05$) were observed at all time points compared to baseline, including up to 13 days after last application. (C) Significant reduction ($P<0.05$) in the TEWL were observed during all time periods of the treatment phase of the study (Days 3,7,14,21) and during days 22, 24, 30, and 32 of the regression phase when compared to the baseline mean score. There were no significant improvements on days 28 and 34 of the regression phase of the study when compared to baseline. A decrease in TEWL values is indicative of an improvement of barrier function.



Dry skin is a common condition on the legs, particularly developed during winter and is often correlated with impaired barrier, decreased stratum corneum hydration and increased TEWL.[20] Our clinical study demonstrated that treatment of individuals with moderate to severely dry skin with the colloidal oatmeal protectant lotion was effective in significantly restoring the skin barrier, improving visual dryness and moisturization of dry skin. In addition, skin benefit continued for up to 13 days after the last application in the regression phase of the study. Clinical evaluations of skin dryness showed significant improvements ($P<0.05$) at all time points during the treatment and regression period, including 13 days after the last application. Skin was significantly more hydrated ($P<0.05$) at all time periods measured during both the treatment and regression period. At the end of the regression phase (2 weeks no treatment) mean moisturization values were still significantly higher than baseline. All these changes were accompanied by significantly improved TEWL values at all time points during the treatment period and up to day 9 of the regression (no treatment) phase of the study indicating that the colloidal oat treatment was effective in restoring the skin barrier.

The acid-mantle in skin of individuals with atopic dermatitis or compromised skin has been found to be disrupted, resulting in an elevated skin pH in those individuals.[21-23] Previous studies have demonstrated that colloidal oats can buffer skin pH in subjects with either dry skin dermatitis or individuals with atopic dermatitiss.[4] The pH-buffering capacity of colloidal oat fractions demonstrated that the water fraction (WCO) which is rich in water-soluble oat proteins (globulins and prolamines) and carbohydrates, demonstrated very effective pH buffering activity (Table 2). These findings support the notion that oat proteins may directly contribute to the skin barrier benefits of colloidal oatmeal. The use of colloidal oats for skin irritation and compromised skin barrier has been well documented. Only recently studies have determined the mechanisms of action of how colloidal oatmeal can reduce inflammation and restore skin barrier.[7] The current study demonstrates in vitro that the colloidal oatmeal increased expression of genes for skin barrier protein and skin lipid, which could contribute to improved skin barrier. And finally a colloidal oatmeal skin protectant lotion yielded significant clinical improvements in visual skin dryness, skin moisture, decreased TEWL and therefore improved the skin barrier, suggesting that colloidal oatmeal can exert beneficial effects on skin barrier through the enhancement of barrier homeostasis. Taken together, these results demonstrate that oatmeal-containing lotions can restore skin barrier thereby providing benefits for dry and compromised skin.

DISCLOSURES

Funding sources: Studies were supported by Johnson & Johnson Consumer Companies, Inc. Skillman, New Jersey, USA.

Drs. Olha Ilnytska, Simarna Kaur, Suhyoun Chon, Kurt A. Reynertson, Khalid Mahmood, and Michael D. Southall and Judith Nebus and Michelle Garay are employees of Johnson & Johnson Consumer Companies, Inc. Skillman, New Jersey, USA.

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