

Systematic review of cosmetic benefit of topical application of ferment filtrate

Revisão sistemática do benefício cosmético da aplicação tópica de fermento filtrado

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ABSTRACT

Ferment filtrate (FF), a by-product of nutrient-rich yeast, is believed to be used cosmetically in East Asia since the 1970s. We systematically reviewed the topical effects of ferment filtrate on skin health and determined limitations in the available studies. Recent literature has shown evidence in reducing the baseline fluctuation of pore size, roughness, hyperpigmentation, and redness. However, these studies are limited in efficacy due to their small sample size, their confounding variables, and their limited generalizability. Because of the increase of cosmetic products containing this ingredient, critical analysis of the available and future literature is necessary to prevent consumer misinformation.

Keywords: Skin Diseases; Administration, Topical; Cosmetic Technology; Cosmetic Techniques

RESUMO

O filtrado de fermentação, (FF), um subproduto de leveduras rico em nutrientes, é usado cosmeticamente no leste da Ásia desde a década de 1970. Revisamos sistematicamente os efeitos deste ativo tópico na saúde da pele e determinamos as limitações nos estudos disponíveis. A literatura recente mostrou evidências na redução da flutuação do tamanho dos poros, e também da aspereza, hiperpigmentação e vermelhidão. No entanto, esses estudos são limitados em eficácia devido ao pequeno tamanho da amostra, variáveis de confusão e capacidade limitada de validação externa. Devido ao aumento de produtos cosméticos contendo esse ingrediente, é necessária uma análise crítica da literatura disponível e futura para evitar a desinformação do consumidor.

Palavras-chave: Doenças de pele; Administração Tópica; Tecnologia Cosmética; Técnicas Cosméticas

Review Article

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INTRODUCTION

East Asian skincare has historically used many naturally derived products, touting their anti-aging, anti-inflammatory, and antioxidative properties, treating diseases including eczema and psoriasis.¹⁻⁶ With the event of commercial skincare products and globalization, skincare brands have integrated these traditional skincare ingredients into widely available products for our use, one of which is ferment filtrate (FF), the processed by-product of yeast fermentation.⁷⁻¹⁰ Believed to be discovered in Japan during the 1970s by the founders of SK-II, a prominent cosmetic brand in Japan, FF supposedly provided restoration and youthfulness to the hands of factory workers that processed fermented products, such as sake.¹¹ SK-II became a commercially available brand in 1980 and sold the first widely advertised and distributed FF, a by-product of *Galactomyces*, named Pitera™.¹¹

Since then, different variations of FF have been developed and sold in different cosmetic brands. According to INCIdecoder, an online website that analyzes cosmetics by their ingredients, there are over a hundred products containing a form of FF.¹² *Galactomyces* FF remains the most common type of FF found in these products.¹² Also, these products typically have market FF directly in the name of the product and tout the percentage of FF used for their formulations to entice their consumers.¹² The habits of these brands lend credence to the idea that FF has been increasingly used by cosmetic consumers, especially in Asian markets. The Fortune Business Insights estimates that the skincare market will increase from USD 133.90 billion in 2018 to USD 200.25 billion by 2026, with a significant share held by the Asia Pacific.¹³ The home of SK-II, the founder of FF, Japan released a statement through its Cosmetic Industry Association claiming that skincare products held the largest market share in the country, including around 50.1% of total cosmetic shipments in 2018.¹³ With the increase of disposable income in countries in the Asia Pacific, the Asian market is exponentially expanding, creating the perfect environment for the large demand for skincare products that contain FF.

In this high-demand market, FF is extensively marketed in skin products as a comprehensive “miracle” ingredient that can solve several skin issues. SK-II advertises that the Pitera™ contains over “50 micronutrients” that “soften texture, reduce the appearance of dark spots and fine lines due to dryness, even the look of skin’s tone, and enhance visible radiance”.¹⁴ Other claims include “brightening”,¹⁵ “hydrating”,¹⁵ “hyperpigmentation”,¹⁶ and “basic strength symptoms”.¹⁶ Regarding other marketing terms, skin products also advertise to decrease sebum production, minimize pore size, provide an anti-aging effect, improve acne, and provide sustained hydration of the skin.

Along with the ubiquity of FF and its laudatory advertising, there is limited research on the mechanism of action of FF, and most of the current research focuses on bacterial fermentation instead of yeast fermentation, the latter is much more widely available in the cosmetic market. Fermentation by *Cutibacterium acnes*, probiotic lactic acid bacteria, and *Lactobacillus*

created propionic acid, polyphenols, flavonoids, and lactic acid, potent tyrosinase kinase inhibitors in melanoma cells, reducing pigment production *in vitro*.¹⁷⁻¹⁹ Bacterial fermentation has also been found to increase the antioxidant activity of plant extracts and induce Akt/ERK/GSK-3 β signaling pathway to theoretically promote hair growth.^{20,21} While a plethora of publications detail the mechanisms of FF created by bacteria, FF created by yeast strains is not as well researched but much more widely available to the market. Current literature details that *Galactomyces* FF decreased the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), which is an oxidative stress marker, indicating that FF produced by yeast can potentially have antioxidant properties.²² It was supported by another article that showed the reduction of reactive oxygen species (ROS) in the human skin equivalent model after the application of Pitera™.²³ Even so, there is sparse literature on testing yeast FF *in vivo* and no publications that consolidated the current information available and determine its benefits and limitations.

There are few scientific studies investigating the *in vivo* effect of FF. Current literature suggests some efficacy in reducing hyperpigmentation by decreasing melanin synthesis while strengthening the skin barrier, reducing acne, and limiting sebum production. Even with this preliminary evidence supporting the use of FF in cosmetics, the current body of literature has never been consolidated or analyzed for validity. In this study, we aimed to find all papers assessing the topical effects of FF, ascertain its potential benefits and harmful effects on skin health, determine limitations in the studies, and apply this knowledge to a wider understanding of potentially misleading marketing claims.

METHODS

To ensure that we covered all possible publications regarding the topic of interest, we searched Pubmed using 48 possible search terms using Boolean operators (Table 1). Once the search terms were used, all consequent literature was identified, and duplicates were deleted. The literature that was analyzed after this point was updated on April 28, 2022.

Our inclusion criteria included: clinical trials measuring the topical use of fermented products on the skin *in vivo*, including animal and human, published at any point in time. Exclusion criteria included: trials without a vehicle or control; trials that mainly focused on *in vitro* and ex vivo results; trials that mainly focused on histological parameters. All duplicates were identified and excluded to ensure that all publications were analyzed only once. After the removal of duplicates, 113 papers were identified using this method. Abstracts were screened to determine the papers’ relevance and extraneous papers were removed. Thus, we found five relevant papers to the inclusion criteria.

The list of publications was read for their content and screened again, leading to the final list of papers. These papers were analyzed for different aspects, including species tested, method of application, the proposed mechanism of action, and

TABLE 1: List of the keywords that were used to find the literature used in this study

Ferment filtrate skin★	Galactomyces dermat★	“saccharomyces” “topical” cosmetic★
Ferment filtrate derm★	Galactomyces cosmetic★	“saccharomyces” “topical” hair★
Ferment filtrate cosmetic★	Galactomyces hair★	“saccharomyces” “topical” nail★
Ferment filtrate hair★	Galactomyces nail★	“saccharomyces” “topical” beaut★
Ferment filtrate nail★	Galactomyces topical★	Bifida ferment lysate skin★
Ferment filtrate topical★	Galactomyces beaut★	Bifida ferment lysate derm★
Ferment filtrate beaut★	Pitera skin★	Bifida ferment lysate cosmetic★
Ferment lysate skin★	Pitera derm★	Bifida ferment lysate hair★
Ferment lysate derm★	Pitera cosmetic★	Bifida ferment lysate nail★
Ferment lysate cosmetic★	Pitera hair★	Bifida ferment lysate topical★
Ferment lysate hair★	Pitera nail★	Bifida ferment lysate beaut★
Ferment lysate nail★	Pitera topical★	
Ferment lysate topical★	Pitera beaut★	
Ferment lysate beaut★	“saccharomyces” “topical” skin★	
Galactomyces skin★	“saccharomyces” “topical” derm★	

significant benefits and harms. Certain trends were also noted, as well as limitations and suggestions made by the articles. The information from these papers was compiled and consolidated, and limitations and potential future research were analyzed.

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Figure 1 shows the PRISMA flow diagram, modified with our data, that we followed to find the articles shown here.

RESULTS

Types of Publications

The systematic review included a total of five publications that fit the criteria.^{24–28} The study designs of these five publications are: double-blind, placebo-controlled, randomized clinical trial; human clinical trial over two weeks, with no information regarding blinding and the placebo consisting of basal skin state; single-blind, placebo-controlled, crossover study with no longitudinal follow-up; 8-week clinical study with no information on blinding; and a two month randomized controlled trial, with no information on blinding.^{24–28} The maximum sample size was 105 young Japanese women, with a maximum age range of 19–49 years old, and a maximum Fitzpatrick skin type range of III to V.^{24–28} The length of the studies ranged between 10 minutes and eight weeks.^{24–28} Confounding variables commonly cited included Total Epidermal Water Loss (TEWL). Two of the five studies tested FF in combination with other ingredients, including brightening ingredients such as niacinamide, alpha arbutin, tranexamic acid, dexpanthenol, and *Centella asiatica* extract.^{27,28}

FF decreased hyperpigmentation development

Two randomized controlled trials reported the use of FF in combination with other agents such as tranexamic acid (TA),

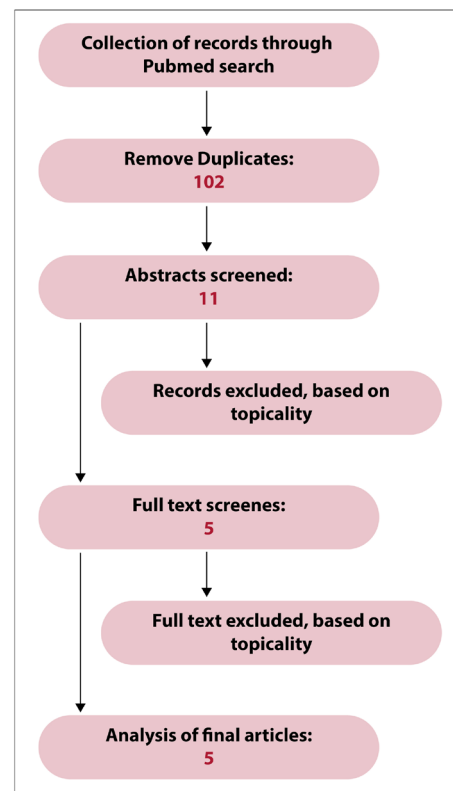


FIGURE 1: Exophytic, pinkish, well-defined tumor on the plantar region of the left foot, with adjacent erythematous-crust plaque

alpha arbutin, *Centella asiatica*, and dexpanthenol to assess the effectiveness of these ingredients in decreasing hyperpigmentation development. One of the studies was a three-arm randomized controlled trial including three different treatment groups: a TA 3% combination serum (3% TA, 4% *galactomyces* ferment filtrate

[GFF], 2% niacinamide, and 4% alpha arbutin) treatment group, a TA 2% combination serum treatment group, and a hydroquinone 4% treatment group.²⁷ This study comprised 44 subjects aged 25–50 years with a Fitzpatrick skin type ranging from III to V evaluated for four weeks.²⁷ All treatment groups displayed significant improvement in skin brightness and hyperpigmentation after four weeks ($p > .001$).²⁷ Also, no significant differences were found between the TA treatment groups, which included FF and hydroquinone ($p < 0.05$).²⁷

The other study was a double-blind, placebo-controlled, randomized clinical trial investigating the effectiveness of a combination serum-containing GFF, dexpanthenol, and *Centella asiatica* to treat post-acne hyperpigmentation (PAH).²⁸ It involved 51 non-pregnant women with PAH and Fitzpatrick skin types (FST) IV–V divided into treatment ($n=27$) and placebo-controlled ($n=24$) groups.²⁸ The trial assessed the subjects every two weeks and tracked the results based on a melanin index (MI) and Lightness (L) score. The treatment group demonstrated a consistent increase in L score and a decrease in MI ($r > 0.9$, $p < 0.05$).²⁸ Also, subjects with FST IV demonstrated a significantly lower MI than placebo after eight weeks ($p < 0.05$).²⁸

Overall, these studies showed that FF combined with other actives is as effective as the standard hydroquinone 4% to treat hyperpigmentation.²⁷ Also, the studies indicated a generally better result in reducing post-inflammatory hyperpigmentation and increasing skin brightness than a placebo.²⁸

FF decreases pore size appearance and skin roughness

A clinical study by Miyamoto investigated the efficacy of 3 mL GFF in the form of Pitera™ topical application through a self-facial imaging system (eMR Pro). It found that, after the application, pore size, roughness, and redness values significantly reduced.²⁵ The study involved two separate studies, comprising 105 young Japanese women taking facial images three times a day: in the morning after waking up, in the morning after washing the face, and in the evening after washing the face.²⁵ Both studies 1 and 2 demonstrated a significant reduction in pore size and facial roughness in the morning after washing the face and in the evening after washing the face compared to the baseline (in the morning after waking up; $p < 0.01$).²⁵ Also, delta fluctuation of redness was significantly reduced through GFF treatment from week 1 to week 4 compared with the baseline period from week –4 to week –1 ($p < 0.01$). Overall, even though there may be daily fluctuation in skin texture, there was a significant net change in the reduction of redness, pore size, and skin roughness.²⁹

FF has anti-inflammatory properties

One particular human clinical study investigating the anti-inflammatory properties of the topical application of a dried *Saccharomyces Cerevisiae* ferment demonstrated a reduced level of histamine-induced skin inflammation.²⁴ This single-blind, placebo-controlled, crossover study included 12 volunteers (five men, seven women), considered in good health. Utilizing a non-invasive Doppler probe (PeriFlux 5000), the study analyzed the time to

maximum blood perfusion, irritation, and speed of inflammation resolution on blinded subjects.²⁴ Following the histamine-induced inflammatory response, all subjects, except one with sensitivity to yeast, reported less itching and burning on sites treated with dried ferment compared to the saline procedure.²⁴ In all treated subjects, the time needed for the histamine-induced increase in blood perfusion to the plateau was significantly reduced ($P < 0.05$).²⁴ Also, the speed of inflammation resolution was reduced compared to control saline-treated sites ($P < 0.05$).²⁴

FF suppressed Transepidermal Water Loss

With the recent COVID-19 pandemic, “maskne” or comedonal inflammation that occurs from mask use, has become prevalent in the population, presumably from transdermal epidermal water loss.²⁶ A paper published by Miyamoto’s group showed that mask-wearing significantly increased TEWL fluctuations within a day.²⁶ A two-week observation of 20 healthy Japanese women showed that applying topical GFF moisturizer on mask wearers statistically increased the skin hydration level ($p = 0.005$).²⁶

DISCUSSION

As FF becomes increasingly popular in commonly marketed skin products, it has become crucial to understand the current literature reviewing its effectiveness and safety. Recent literature has shown evidence of the GFF’s effectiveness in reducing the baseline fluctuation of pore size, roughness, and redness that the skin experiences throughout the day.^{24,25} Pore size, skin roughness, and redness were assessed over eight weeks and showed a strong association with increased skin aesthetics over time, but these findings were only determined in Japanese-descent young (between 22–34) women and with a small sample size ($n=48$).²⁹ While evidence of decreased inflammation is stronger due to the placebo-controlled, crossover study involving both women and men with a wider age range of 19–49; still, the sample size was small ($n=12$), no FF longitudinal study was conducted, and the subjects were all in exceptional health, with no depressive, diabetic, or allergic diagnoses.²⁴ These factors limit the generalizability of the studies. However, the current evidence for FF’s aesthetic effects on the skin is promising.

Additionally, FF was found to attenuate sebum production, increase skin barrier-related proteins, attenuate oxidative stress, and decrease redness through its potent antioxidative agonist properties for aryl hydrocarbon receptors.²⁵ Several randomized controlled trials have supported the FF’s effectiveness as a depigmenting agent when used in conjunction with particular combination serums.²⁷ One study assessing serum containing FF combined with tranexamic serum, alpha arbutin, and niacinamide showed it was as effective as hydroquinone 4%, the gold standard depigmenting agent, in a healthy population.²⁷ Another randomized control trial study used a serum combination of GFF, dexpanthenol, and *Centella asiatica* to treat post-acne hyperpigmentation (PAH) in subjects with Fitzpatrick skin types IV and V. This multi-serum combination showed notable

improvement in skin brightness and PAH reduction compared to placebo.²⁸ These articles showed potential efficacy in the cosmetic effects of topical FF on the skin as a strong depigmenting ingredient to treat hyperpigmentation that could be as potent as hydroquinone, especially in conjunction with other ingredients. With data supporting the synergistic use of FF with other ingredients, it can be an adjunctive booster for currently well-established skin brighteners, moisturizers, and pore-reducers. It is noteworthy that future studies with longer follow-up durations will serve an essential role in establishing the clinical significance of adding multiple substances in augmenting the depigmentation effect. Although the literature supports the depigmenting effects of GFF through inhibiting tyrosine hydroxylase and its antioxidative properties, its effect was not quantified alone, and further research is necessary to understand better the individualized role of GFF in the depigmentation process.

While these papers show initial promise of FF's efficacy with topical use, there are significant limitations to these studies. Each of the papers is prone to small sample sizes, and some have as few as 12 total subjects, limiting their generalizability and increasing their risk of error. These studies are also brief, and the longest has a duration of around eight weeks.²⁸ Any long-term benefits or harm are undocumented, untested, and not discussed within the papers, and data regarding the mechanism of action, including absorbability and biochemical mechanisms *in vivo*, is sparse and prevents any extrapolations. Also, the only randomized control trial performed to date involve a serum combination containing FF and other proven compounds for hyperpigmentation. Thus, further research is necessary to determine the singular depigmentation effect of this ingredient.^{27, 28}

Through the analysis of these studies, FF as a booster ingredient seems to be a potential ingredient that might benefit users, in particular those who seek treatment for hyperpigmentation. In conjunction with the limitations of the studies, these papers do not address many claims present in marketing for commercial products containing FF, including terms such as “anti-aging” and “anti-acne.” Research addressing these discrepancies may provide helpful information on how marketing claims could misconstrue currently available evidence to the public.

CONCLUSION

The limited literature exploring FF in skin products supports its potential effectiveness in reducing hyperpigmentation, strengthening the skin barrier, decreasing acne, and reducing sebum production. However, the data mainly support the FF use as a booster ingredient to increase the synergistic power of other anti-pigment compounds. Also, FF adverse events are not typically tested, addressed, or extrapolated in the current literature. By expanding research to include large-scale studies with diverse subject populations, increased sample sizes, and more longitudinal research, FF could potentially become established as a cosmetically enhancing skincare ingredient. Due to the saturation of cosmetic products that tout bold claims available to consumers, it is essential to continue to obtain and critically analyze the available literature regarding FF. Future papers should include large-scale studies involving varying effects of hyperpigmentation, larger sample sizes, and longer follow-up durations to further establish the clinical significance of GFF and explore the effect of marketing claims in misinforming the public.²⁸ ●

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