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REVIEW

The potential cutaneous benefits of *Tremella fuciformis*

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Abstract
Tremella fuciformis, also known as snow mushroom, is an edible mushroom that has historically been popular in herbal and Asian medicine and cuisine. The main polysaccharide ingredients have been extracted and used as treatment in a variety of conditions, demonstrating positive effects in a range of biological functions including those involved in antioxidation, antitumor, antidiabetic, immunomodulatory, and neuroprotective pathways. Studies have demonstrated the role this extract may play in skin antiaging, photoprotection, wound healing, and barrier protection. Most studies have been limited to in vitro and in vivo animal models. Future clinical research is needed to further understand the role of *T. fuciformis* in dermatology. This review will discuss the existing research findings and potential future applications for *T. fuciformis* as a treatment in skin conditions.

Keywords *Tremella fuciformis* · Snow mushroom · Tremella fuciformis polysaccharides · Antiaging · Photoprotection · Wound healing

Introduction

Tremella fuciformis is an edible mushroom that has historically been popular in herbal and Asian medicine and cuisine [1, 2]. This fungus, also known as snow mushroom, snow fungus, and white jelly mushroom, consists of polysaccharides as its main ingredient [1, 3]. The five main polysaccharides in the mushroom are acid heteropolysaccharides, neutral heteropolysaccharides, cell wall polysaccharides, extracellular polysaccharides, and acid oligosaccharides [4]. These *T. fuciformis* polysaccharides (TFPS) can be extracted and used as treatments in a variety of conditions [1]. TFPS has demonstrated positive effects in a range of biological functions including those involved in antioxidation, antitumor, antidiabetic, immunomodulatory, and neuroprotective pathways [1, 2, 5–9]. In 2002, TFPS was approved by the Chinese Food and Drug Administration (SFDA) for the treatment of cancer patients with leukopenia induced by chemotherapy and radiotherapy [6]. Recently, research has begun to examine the role TFPS may have in dermatology.

As a potentially strong antioxidant, TFPS may be able to provide a variety of cutaneous benefits. There is strong demand for safe and effective skincare products. The global skincare market size was estimated to be 98.83 billion USD in 2020 and is projected to grow to over 145 billion USD by 2028 [10]. There is a drive for natural ingredients and products that can deliver results with minimal unwanted side effects [10]. TFPS may be able to help fill this unmet demand.

Most research to date has focused on in vitro and in vivo animal models. These studies demonstrate promising results, elevating the potential for this traditional ingredient to serve as a new treatment agent in dermatology. Herein, this review will discuss the research findings for TFPS as a treatment for skin conditions. The potential applications for TFPS in dermatology include antiaging, sun protection, wound healing, and barrier protection/enhancement.

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Antiaging

TFPS has the potential to serve as an antiaging agent. Aging, including photoaging induced by damage from solar radiation exposure, can result in rhytids, atrophy, roughness, and pigment discoloration [11]. Cumulative damage to the skin contributes to these manifestations. Studies have demonstrated that this type of damage can result from reactive oxygen species (ROS) formation leading to downstream negative effects [12]. ROS incite inflammatory cytokines and cycles of inflammation lead to protein and DNA damage as well as apoptosis in dermal cells [12]. Antioxidants scavenge ROS to prevent them from activating and triggering these damaging pathways [12, 13]. Thus, antioxidants may help mitigate the downstream effects induced by ROS to prevent processes that contribute to aging and pathologies [12, 13].

TFPS has antioxidant properties that can inhibit oxidative stress and cell injury [1, 4, 5]. In one study, researchers exposed human dermal fibroblasts (HDFs) to hydrogen peroxide (H_2O_2), an ROS that interacts with intracellular copper and iron resulting in further increases in other ROS, DNA damage, protein damage, decreased cell viability, and apoptosis [1]. H_2O_2 represents one of many ROS that may contribute to aging and pathologies [1]. HDFs were pretreated with TFPS extract prior to exposure to H_2O_2 injury and compared to HDFs exposed to H_2O_2 injury alone [1]. Results showed that treatment with TFPS overall had a positive effect on the cell viability compared to control in a dose-dependent manner [1]. Treatment attenuated H_2O_2-induced ROS generation by 51.7% compared to untreated cells [1]. Cells treated with TFPS had decreased apoptosis, decreased activation of pro-apoptosis pathways, and increased activation of pro-survival pathways [1]. Western blot analysis further supported the conclusion that TFPS mitigates injury by showing that treated cells had decreased expression of H_2O_2-induced pro-apoptotic proteins including p16, Bax, ap53, and caspase-3 compared to control [1]. SIRT1 expression also increased in TFPS treated cells [1]. SIRT1 is a sirtuin, which has protective functions in DNA stabilization and antiaging processes [1, 14]. SIRT1 attenuates H_2O_2-induced oxidative stress and apoptosis [1]. The increase in SIRT1 expression elucidates a central pathway in which TFPS protects fibroblasts from damage [1].

An in vitro animal study in rats further explored the potential for TFPS to specifically prevent ultraviolet (UV)-induced photoaging [15]. Rats were given an oral treatment of TFPS and then exposed to UV radiation [15]. Overall, the treatment demonstrated protective effects on the skin [15]. Histologic analysis showed decreased signs of aging and damage, including decreased epidermal hyperplasia, hemorrhages, diffuse inflammatory sites, and fiber disorganization in the dermis [15]. There was increased types I and III collagen content in the treated group compared to the untreated group, suggesting that TFPS may play a role in preventing collagen loss, a major contributor to skin aging [15]. Researchers also examined glycosaminoglycan (GAG) content, which can be induced by UV radiation and alter the structure of dermal connective tissue, damage collagen, and damage surrounding structures [15]. The study found that TFPS treatment decreased the total GAG content compared to the control, further demonstrating antiaging effects. In addition to collagen, elastin and hyaluronic acid were also increased in the dermis in a dose-dependent manner in response to TFPS treatment [15]. These all contribute to the structural integrity of the dermis, playing essential roles in antiaging [15].

The potential for TFPS to mitigate the effects of aging can be understood through its antioxidant properties. In vitro and in vivo studies have demonstrated the possible pathways that TFPS may be able to restore balance in the skin through the activation of pro-survival pathways and suppression of pro-apoptotic pathways, oxidative stress, and cell injury [1, 15]. Further clinical research is warranted to evaluate whether these effects can be translated into safe and effective treatments in humans.

Photoprotection

By analyzing how TFPS may potentiate the effects of UV-induced photoaging, researchers have also elucidated a possible role for TFPS as sun protection. In the previously discussed animal study, results showed that pretreatment with oral TFPS attenuated the initial damage induced by UV radiation that results in signs of sunburn [15]. Macroscopic analysis revealed that TFPS treatment alleviated erythema, dryness, and escharosis after UV exposure [15]. Researchers further measured the activity of antioxidant enzymes, including SOD, GSH-Pe, and CAT [15]. They found that the activity level of these enzymes were increased in the TFPS-treated group compared to the control, demonstrating a possible mechanism for the overall protective pathway [15]. The demand for sun protection products continues to grow as patients become more aware of the damaging effects of solar radiation and more interested in preventing the clinical signs of photoaging [13]. There is a demand for safe and effective sunscreens that do not leave unwanted side effects, including a white cast on the skin, greasy/oily textures, or pilling on the skin [13]. An oral sunscreen option, like the one studied in the animal model, holds the potential to offer these benefits and may be of particular interest to persons of color, who particularly suffer from the negative appearance of a white cast.

An in vitro study specifically examined the effects of TFPS on UVA-induced photodamage in HDFs [4]. Researchers found that TFPS increased cell viability in a dose-dependent manner [4]. TFPS treatment reduced UVA-induced ROS generation and lipid oxidation while also increasing the antioxidant activity and capacity of cells [4]. The study examined the pathways that are specifically activated to combat UVA radiation, including the NrF2 pathway [4]. NrF2 is activated by UVA-induced ROS and works to enhance antioxidant function in cells [4]. Treatment with TFPS resulted in the upregulation of this pathway leading to increased antioxidant gene expression [4]. The researchers concluded that TFPS inhibits UVA damage in HDFs by activating this and other related pathways, further demonstrating the potential for TFPS to serve as a sun protection agent [4]. Furthermore, researchers noted that TFPS had no toxic effect on the cells [4]. This importantly demonstrates the safety and potential high tolerability of this treatment.

Wound healing

TFPS may also have a role in wound healing, including mitigating the effects of fibrosis, scarring, and post-inflammatory hyperpigmentation (PIH). A study performed on human dermal fibroblasts and keratinocytes found that TFPS promoted cell migration [2]. Cell migration is essential to wound healing. Increased migration can serve to accelerate healing [2]. Timely healing can lead to better aesthetic outcomes including decreased scarring and decreased PIH [2].

In a study examining in vitro mouse B16F10 cells (melanoma cell line), researchers found that TFPS decreased melanin content via suppression of tyrosinase expression, the rate-limiting enzyme in melanogenesis [2]. This demonstrates the potential for TFPS to be used in the treatment of hyperpigmentation and the prevention of pigmentation in scar tissue [2].

As previously discussed, studies have also demonstrated the ability of TFPS to prevent damage in HDFs [1, 4]. Injury and over-proliferation of HDFs can lead to fibrosis in the skin. By enhancing antioxidant activity and minimizing ROS damage in fibroblasts, TFPS may be able to limit the progression of fibrosis.

Skin barrier protection/enhancement

TFPS may also have a role in enhancing the barrier protection of skin, providing potential treatment options for atomic dermatitis (AD) and xerosis. One study evaluated the use of both topical and oral formulations of TFPS treatment in mice affected with AD [5]. AD is a chronic, inflammatory disease that manifests with symptoms of pruritis, dryness, and eczematous skin lesions due to an imbalance of Th1 and Th2 responses [5]. The disease leads to skin barrier dysfunction which can cause water loss in the skin and an increase in pro-inflammatory cytokines [5]. Treatment with TFPS alleviated the severity of AD in the mice, which was evaluated through a variety of measures including gross inspection, H&E staining, flow cytometry, and immunohistochemistry [5]. Treatment reduced the inflammatory response assessed by immunohistochemistry. Results showed that TFPS decreased TNF-α and IFN-γ while increasing regulatory T cells, including CD4, CD25, and Foxp3, which help to regulate overactive immune responses [5]. The mice showed a decrease in transepidermal water loss, a decrease in swelling of affected sites, and suppression of epidermal thickness and mast cell infiltration [5]. Overall TFPS treatment led to improved skin barrier function through suppression of transdermal water loss, epidermal thickening, and edema [5].

Current treatments for AD include creams, UV light, and systemic therapy [16]. While topical treatments may not provide satisfactory resolution of symptoms, UV light and biologics carry risks such as carcinogenesis and immunosuppression, respectively [16]. The potential for a safe, natural treatment that has shown promising results in an animal model in both topical and oral forms could offer the up to 20% of children and 3% of adult patients worldwide who suffer from AD a new way to relive their symptoms and improve their disease state [17].

In one study evaluating the safety and efficacy of TFPS as a moisturizing agent in hand sanitizer in humans, researchers found that this ingredient demonstrates moisturizing properties [3]. Measurements and calculations determining the skin capacitance and skin hydrating efficacy showed that TFPS enhanced barrier protection and moistened skin compared to sanitizers without TFPS [3]. Additionally, TFPS was found to be non-irritating, further supporting its favorable safety profile [3]. The ability of TFPS to suppress water loss in the skin, improve barrier function, and moisturize the skin demonstrates the potential for this ingredient to treat a variety of skin conditions where these functions are suboptimal.

Conclusion

TFPS has demonstrated a variety of effects throughout the body, including antioxidant, anti-inflammatory, antitumor, neuroprotective, antidiabetic, antihypercholesterolemic, and immunomodulatory effects [1, 3, 4, 15]. The few studies that have evaluated the potential use for TFPS in the skin have shown promising results. TFPS may theoretically be able to provide skin antiaging treatment, photoprotection, improved wound healing, and enhanced barrier protection. Most of these studies have been conducted through in vivo and in vitro animal models. Future clinical research

is needed to further study the safety and efficacy of TFPS in humans and further elucidate applications of this treatment. Natural, organic products are in high demand [10, 13]. TFPS has long been used in Chinese and other cultures for medicinal and culinary purposes [2, 18, 19]. Based on preliminary research, this extract holds the potential to treat a variety of dermatological conditions in a manner that is safe and effective for patients.

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Data availability The data that support the evidence presented in this article is accessible from public databases including PubMed.

Declarations

Conflict of interest The authors declare no competing interests.

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