SKIN

IN-DEPTH REVIEW

The Therapeutic Potential of Withania somnifera (Ashwagandha) in Non-Malignant Dermatological Conditions

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ABSTRACT

Introduction: Withania somnifera (WS), or Ashwagandha, is revered for its anti-inflammatory properties. While widely recognized for its systemic health benefits, including immunomodulatory and antioxidant effects, its dermatological applications remain underexplored. This review aims to address this gap by analyzing evidence on WS's potential mechanisms, therapeutic uses, and limitations in non-malignant skin conditions.
Methods: A literature search was conducted on Ashwagandha using the PubMed, Google scholar, and Scopus databases and the cited literature in articles initially retrieved. A combination of the following keywords were used: Withania somnifera, Ashwagandha, Withaferin, dermatology, skin, hair. Among the results, 18 articles met the inclusion/exclusion criteria and were included in the review.
Results: Several studies highlight WS's potential to treat pigmentary disorders, improve skin aging, manage inflammatory skin conditions, promote wound healing, and support hair and scalp health. WS's phytochemical composition, particularly its withanolides and phenolics, contributes significantly to its therapeutic effects.
Conclusion: WS shows significant potential in dermatology. It offers antioxidant, anti-inflammatory, and adaptogenic benefits and has a strong safety profile. While preliminary evidence is promising, further research is essential to establish its role in dermatology.

INTRODUCTION

Cosmeceuticals are bridging the gap between cosmetics and pharmaceuticals. These products, which combine plant-derived substances known as adaptogens, target the underlying mechanisms of skin aging and pathology, such as oxidative stress and inflammation.[1] As research progresses, advancements in biomarker technology and clinical trials are providing valuable insights into how cosmeceuticals can be tailored to address specific skin concerns.[1]

Withania somnifera (WS), commonly known as Ashwagandha, is a medicinal plant revered in Ayurvedic medicine with historical use dating back over 3000 years.[2] It is classified as a rejuvenator and a potent adaptogen with anti-inflammatory properties. In recent years, there has been a surge of

interest in the health benefits of ashwagandha and its components. Many studies have demonstrated its anti-stress, anti-inflammatory, neuroprotective, immunomodulatory, antibacterial, anticancer, antidiabetic, and cardioprotective activity.[3,4] The rising popularity of WS is reflected in its commercial success; in 2020, sales increased by 185.2%, amounting to $31.7 million and ranking it as the 12th top-selling herbal supplement in the United States.[5]

WS's therapeutic effects are attributed to its rich composition of phytochemicals, including withanolide alkaloids, steroids, flavonoids, saponins, phenolics, and glycosides.[3] Among these, withanolides and phenolics are considered to be the most significant contributors to its therapeutic properties. Withanolides have immunomodulatory activity, while phenolic compounds have antioxidative properties.[4] The root of WS contains the highest concentration of alkaloids, along with other bioactive compounds such as phenolics, flavonoids, and fatty acids.[6] Due to this rich phytochemical profile, WS root extract is predominantly utilized in most studies investigating its therapeutic effects.

Despite its widespread use and recognition in systemic health, the potential applications of WS in dermatology remain underexplored. This paper aims to fill this gap by providing a literature review on the utility of WS in dermatology.

METHODS

A literature search was conducted on WS using the PubMed, Google Scholar, and Scopus databases and the cited literature in articles initially retrieved. A combination of the following keywords were used: Withania somnifera, Ashwagandha, Withaferin, dermatology, skin, and hair. Only literature in English pertaining to non-malignant dermatology was included. Literature where WS was used in combination with other supplements was excluded. The search yielded 26645 results across the databases, of which, 18 met inclusion and exclusion criteria and were included for review.

RESULTS

Pigmentation Disorders

Hyperpigmentation

WS has shown significant potential in the treatment of hyperpigmentation. WS extract (WSE) and its bioactive compound, Withaferin A (WFA), exhibit a pronounced depigmenting effect by targeting the molecular mechanisms underlying endothelin-1 (EDN-1) and stem cell factor (SCF)-stimulated pigmentation.[7,8] WSE significantly reduced EDN-1 induced pigmentation and eumelanin content in human epidermis equivalents at a concentration of 10 µg/mL.[7] This was evidenced by suppressed expression of melanocyte-specific mRNAs and proteins, thereby suggesting an effect on intracellular signaling upstream of gene expression.[7] The protein kinase C/mitogen-activated protein kinase (PKC/MAPK) pathway is a critical signaling cascade in modulating melanogenesis within human melanocytes.[7,8] WSE treated human melanoma cells in culture also revealed reduced EDN-1 induced phosphorylation of Raf-1, MEK, ERK, MITF and cyclic AMP responsive element binding protein (CREB) 15 minutes post-treatment with EDN-1.[7] A similar effect was observed with WFA at concentrations of 10-50 µm.[7] Given these findings, the authors concluded that WSE preferentially inhibits PKC activity and reduces EDN-1 induced pigmentation.[7,8]

WSE displayed a similar regulatory effect in SCF-induced pigmentation by selectively impairing ERK phosphorylation, leading to reduced melanocytic activity without directly inhibiting tyrosinase.[9] After 14 days of treatment of human epidermal equivalents with WSE, a dose-dependent reduction in SCF-induced pigmentation was observed, which was linked to a significant decrease in eumelanin content.[9] These findings were evidenced by a suppression of melanocyte specific proteins, including tyrosinase.[9] WSE treatment also showed reduced SCF-induced phosphorylation of ERK, MITF, and CREB, but not Raf-1 and MEK, unlike in EDN-1 induced pigmentation.[9,10] Notably, human melanocytes treated with WFA showed attenuated SCF stimulated phosphorylation of c-KIT, Shc, Raf-1, MEK, ERK, CREB and MITF.[9,10] WFA reduces SCF phosphorylation through the inhibition of c-KIT autophosphorylation, without interrupting the binding of SCF to the c-KIT receptor.[10] Therefore, WSE and WFA may reduce SCF induced pigmentation through the preferential inhibition of ERK phosphorylation, given the lack of direct inhibition of tyrosinase activity or direct melanocytic cytotoxicity.[9,10]

Additionally, WSE demonstrated efficacy in UVB-induced pigmentation by reducing EDN-1 secretion from UVB-exposed keratinocytes and interfering with intracellular signaling upstream of tyrosinase gene expression in melanocytes.[8] These findings underscore the potential of WS as a melanogenic signaling-interruption agent for hyperpigmentation conditions, including melasma, solar lentigo, and UVB-melanosis, where overexpression of SCF and EDN1 contributes to the pathology. [7–10] Unlike many depigmenting agents, WS avoids direct tyrosinase inhibition, reducing the risk of hypopigmentation.[8–10]

Hypopigmentation

WS has demonstrated potential in addressing hypopigmentation in a study investigating the melanin dispersing effect of WFA, a bioactive compound of WS, and the lyophilized extract of WS on isolated frog skin melanophores. [11] The results revealed significant melanin dispersion, a process attenuated by atropine and hyoscine but enhanced by neostigmine, suggesting a mechanism mediated by cholinergic muscarinic receptors.[11] Another study examined the skin darkening effects of WSE and WFA on the isolated melanophores of the wall lizard.[12] Similar to the prior study, the skin darkening effects were significant and the observed effects were diminished by atropine and hyoscine and potentiated by neostigmine, suggesting the involvement of cholinergic muscarinic receptors.[12] The authors proposed that WSE and its active compound act as acetylcholine mimetics, promoting melanin dispersion and resulting in skin darkening through the stimulation of muscarinic receptors.[12]

Photoaging

Several studies highlight the potential of WS in mitigating the effects of photoaging. A randomized clinical trial (RCT) demonstrated that topical application of a lotion with 8% standardized WSE significantly improved markers of skin health, including skin wrinkles, pores, hydration, brightness, and pigmentation, in photoaged facial skin after 60 days of treatment.[13] Skin treated with WSE had a significantly greater reduction in physician assessment scoring, which assessed skin wrinkles, pores, hydration/moisture, skin brightness/tone, and pigmentation, indicating a superior outcome compared to placebo ($p<0.0001$).[13] Additionally, WSE resulted in a reduction in transepidermal water loss (TEWL) by 15.12% and enhanced skin hydration and elasticity,

assessed with R^2 ratio, by 20.66% and 16.34%, respectively, over 60 days ($p<0.0001$).[13] Moreover, no significant differences were observed in changes to the melanin index, suggesting a lower risk of unwanted hypopigmentation.[13] Notably, adverse effects were similar in the treatment and placebo groups, underscoring the extract's tolerability.[13] This study was limited by a sample size of 56 individuals and inclusion of Fitzpatrick phototype III-VI, only.[13]

Additionally, a novel approach using photoluminescent carbon dots synthesized from WS carbon dots (wsCDs) demonstrated promising photoprotective properties in vitro.[14] These carbon dots were biocompatible and effectively mitigated UVB-induced oxidative stress and loss of metabolic activity in human skin epidermal cells.[14] They also facilitated rapid wound healing by upregulating TGF-β1 and EGF gene expression in human epidermal cells.[14] The wsCDs exhibited biodegradability, enhancing their suitability for dermatological applications. These findings highlight WSE's multifaceted role in protecting and repairing UV-B damaged skin.[14] The combined evidence from these studies underscores the potential of WS as a multifunctional agent in targeting photoaging.[13-14] Future research on human subjects is needed to further establish its role in the treatment and prevention of photoaging.

Skin aging

Multiple studies have explored WS's multifaceted potential in mitigating skin aging through various mechanisms. One study demonstrated that it significantly inhibited the accumulation of advanced glycation end-products (AGEs) in fibroblasts exposed to methyl-glyoxal (MGO), a key component in cellular senescence.[15] WS upregulated the expression of TGF-β1 expression by upregulating integrin β1 expression, contributing to the generation of extracellular matrix (ECM).[15] WS suppressed matrix metalloproteinase (MMP)-1 and MMP-2, reducing the degradation of ECM.[15] WS can delay skin aging through reduced AGE accumulation and the production and degradation of ECM.[15]

Furthermore, WS has demonstrated antiglycation properties in vitro, preventing collagen cross-linking and AGE formation under glucose-induced stress.[16] In this study, ethanolic extracts of WS, WS root powder, and metformin were incubated with glucose and rat tail tendons for 30 days.[16] Both WS and metformin prevented the formation of AGEs and collagen cross-linking caused by glucose.[16] The ethanolic extract of WS exhibited effects comparable to metformin in preserving collagen structure and reducing AGE production.[16] Of note, while this study was focused on tendon collagen, type I collagen is the most abundant collagen in both skin and tendon.[17]

Another study explored withagenin A diglucoside (WAD), a compound derived from WS, and its protective effects against TNF-α-induced damage in dermal fibroblasts, which contributes to skin aging.[18] WAD inhibited the production of intracellular reactive oxygen species (ROS), which in turn reduced MMP-1 secretion and suppressed type 1 collagen breakdown.[18] This effect is thought to occur through the suppression of pro-inflammatory pathways, specifically by inhibiting MAPK, Akt, c-JUN, COX-2, and NF-κB phosphorylation. WAD also decreased the expression of proinflammatory cytokines, IL-6 and IL-8.[18]

The inhibitory effects of WSE on collagenase activity demonstrate its potential for mitigating collagen degradation. WSE

inhibited 71% of Clostridium histolyticum collagenase (ChC) activity against ECM degradation in tendon, showcasing a concentration-dependent effect, while promoting collagen stabilization and maintaining ECM integrity through the competitive inhibition of ChC activity. [19] Changes in the secondary structure of collagenase were observed.[19] Another study highlighted that while WFA alone had moderate collagenase inhibition (45.7%), and combining it with epigallocatechin gallate, a green tea phytoconstituent, increased inhibition to 79.08%, surpassing the activity of ascorbic acid alone.[20] These findings highlight the potential role WS may have in the preservation of collagen and skin aging.

Skin Inflammation

The anti-inflammatory effects of WSE have been demonstrated in vivo. In human keratinocyte cells, WSE reduced the expression of pro-inflammatory cytokines such as IL-8, IL-6, TNF-α, IL-1β, and IL-12 while increasing the levels of the anti-inflammatory cytokine TGF-β1.[21] The authors attributed this activity to the suppression of NF-κB and MAPK pathways, as it inhibited phosphorylation of p38 and c-Jun N-terminal kinase and prevented the nuclear translocation of NF-κB p65. Similarly, WSE also demonstrated anti-inflammatory effects in mouse models.[21]

Hidradenitis Suppurativa

WS, particularly WFA, shows promise in addressing metabolic syndrome, which plays a significant role in the exacerbation of hidradenitis suppurativa (HS). Multiple preclinical studies have highlighted the antidiabetic, anti-obesity, anti-inflammatory, and antioxidative properties of WS and WFA. In vitro, it has shown to improve glucose metabolism, enhance insulin secretion, protect pancreatic islet cells from cytokine-induced damage, and reduce adipogenesis.[22,23] These mechanisms are mirrored in vivo, where WFA improved glucose metabolism, insulin resistance, and lipid profiles and reduced adipose tissue and body weight gain in murine obesity and diabetes models.[22] WA acted as a leptin sensitivity, induced white adipose tissue browning, and boosted mitochondrial activity, promoting anti-obesity effects. A double-blind RCT with 52 subjects showed reduced food cravings, cortisol levels, and body fat percentage in stressed, overweight individuals after treatment with WS compared to placebo.[22] Given the strong association between metabolic dysfunction and chronic inflammation in HS, WS emerges as a potential therapeutic candidate to mitigate metabolic contributors to HS pathogenesis while reducing its chronic inflammatory burden.[23]

Psoriasis

WS seed oil (WSSO) has demonstrated therapeutic potential in psoriasis-like conditions, particularly due to its anti-inflammatory and antioxidant properties. Fatty acids extracted from WS seeds using supercritical fluid extraction were analyzed via gas chromatography, revealing bioactive components with significant therapeutic effects. [24] In a 12-O tetradecanoyl phorbol 13-acetate (TPA)-induced psoriatic mouse model, topical and oral administration of WSSO substantially alleviated psoriatic symptoms, reducing inflammation-induced edema and improving histopathological scores.[24]

At the cellular level, WSSO inhibited the release of pro-inflammatory cytokines, IL-6 and TNF-α, and decreased NFκB expression in human epidermoid and monocytic cells treated with TPA or lipopolysaccharide (LPS). WSSO also reduced reactive nitrogen species in LPS-stimulated murine

macrophages.[24] The study concluded that fatty acids derived from WS seeds possess strong anti-inflammatory activity and may serve as a promising adjunct for managing psoriasis-like skin disorders.[24]

Scleroderma

WFA has also shown potential as an antifibrotic agent in scleroderma. In one study using a 28-day murine model of bleomycin-induced scleroderma, researchers administered WFA intraperitoneally.[25] Treatment resulted in a significant reduction in dorsal skin thickness, indicating its effectiveness in mitigating skin fibrosis.[25]

WFA was shown to suppress a key pro-inflammatory phase in fibrogenesis.[25] It inhibited the TGF-β/Smad signaling cascade, a critical driver of fibrosis, and repressed the conversion of fibroblasts to myofibroblasts, which are central to ECM deposition.[25] Additionally, the study demonstrated that WFA modulates the FoxO3a-Akt-dependent NF-κB/IKK inflammatory cascade, a chief pathway in the progression of fibrosis.[25] These findings underscore the potential of WFA to disrupt both pro-inflammatory and fibrotic phases of the disease.[25]

Alopecia

The effects of WS have also been explored in the treatment of alopecia. In a prospective, double-blind, two arm, parallel, comparative RCT with 61 participants aged 18-45 years old with mild to moderate hair loss were randomized to WSE or placebo group and assessed over 75 days.[26] A standardized topical WSE serum known as KSM-66 was used with >5% of total withanolide content, consisting mainly of Withastramonolide A, Withanoside IV, Withanolide A, Withanone and <0.1 % of WFA.[26] Product efficacy was assessed using hair health indicators, including the 60 Seconds Hair Comb Test, Trichoscan analysis, Hair Pull Test, Investigator's Global Assessment, and Hair-Specific Skindex-29 for quality of life.[26] Results showed that WSE treated participants had significant improvement in hair shedding, growth, density, and thickness compared to placebo.[26] Hair density increased with WSE topical serum compared to placebo ($p < 0.001$), as did growth ($p < 0.001$) and thickness ($p < 0.001$).[26] QoL scores improved significantly for participants using Ashwagandha compared to placebo ($p = 0.011$).[26] These findings suggest that topical WS can be an effective alternative in the treatment of alopecia.[26]

Further research highlights the importance of formulation and extraction protocols. Two Ashwagandha extracts with different withanolide properties were studied for distinct mechanisms of action.[27] ASH-Ext1 (ASHWITH) is an oral supplement with >12% withanolide concentration and <1.5% WFA. ASH-Ext2 (Reganolide) is a topical formulation with 38-39% withanolide content and 25% of WFA.[27] ASH-Ext1 demonstrated antioxidant activity and Nrf2 signaling modulation in cell models, while ASH-Ext2 increased β-catenin and telomerase reverse transcriptase (TERT) expression in human hair follicle dermal papilla cells, key factors in hair follicle longevity and regeneration.[27]

Safety Profile

WS has demonstrated a favorable safety and side effect profile. Subjects in the previously referenced studies reported no adverse events. In a RCT assessing the safety of WSE, vital signs and various biochemical parameters were monitored over 8 weeks. [28] No significant side effects were observed compared to placebo.[28] Another study evaluated the safety of WSE in male volunteers over a period of four weeks using physical and biochemical parameters, as well as, electrocardiogram, chest x-ray, and

urinalysis.[29] Statistically significant increases were observed at day 31 in total cholesterol by 5.7%, low-density lipoprotein by 14%, and serum T3 by 8%, and decrease in total bilirubin by 23% but the parameters remained within normal limits and the findings were not clinically significant. [29] The treatment was determined to be well tolerated.[29]

DISCUSSION

A key challenge in cosmeceuticals is the variability in the outcomes these products produce. While drugs are tested for effectiveness, herbal supplements often provide more subtle or variable effects. This complexity arises from the lack of standardized dosing, particularly with plant-based ingredients.[1] The potency of these natural materials is influenced by factors such as growing conditions, weather patterns, and soil quality, making it difficult to determine a consistent dose.[1] However, advancements in technology, such as the use of bioreactors, are now allowing for more precise cultivation of these plant materials. In controlled environments, factors like nutrient levels, oxygen supply, and light cycles can be optimized which enhances the predictability of cosmeceutical ingredients.[1]

Additionally, despite the promising evidence, the application of WS in treating both hyperpigmentation and hypopigmentation presents important limitations. Majority of the evidence is preclinical, which may not reliably predict clinical outcomes. The ability of WS to both inhibit and stimulate melanogenesis raises context specific concerns. WS in individuals may produce unpredictable outcomes, such as lightening effects in hypopigmented areas and darkening in hyperpigmented areas. Further studies are needed to determine efficacy for pigmentary disorders in clinical settings.

CONCLUSION

WS demonstrates significant potential in dermatology due to its antioxidant, anti-inflammatory, and adaptogenic properties, alongside a favorable safety profile. Although preliminary studies highlight its efficacy and tolerability, further research, including large-scale clinical trials, is needed to validate its dermatological applications.

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