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Review Article

Naturally occurring antioxidants for treating rosacea

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The use of complementary and alternative approaches in rosacea, a common, yet poorly understood chronic facial condition with an unknown etiology, has continued to grow. Recent studies have implicated oxidative stress in the pathophysiology of rosacea. As a result, there has been increasing interest in evaluating the effects of using naturally occurring antioxidants as therapeutic agents for managing rosacea. We discuss therapeutic applications of grape seed extract (GSE), vitamin C, azelaic acid, and zinc which have been studied for effects on reducing rosacea.

INTRODUCTION

The use of complementary and alternative medicine (CAM) in dermatology has substantially increased in recent years alongside a stronger foundation of research supporting benefits in patient satisfaction and outcomes. CAM treatments may be leveraged in treating rosacea, which is a common, yet poorly understood chronic facial condition with an unknown etiology.[1]

Rosacea is characterized by flushing, temporary or persistent erythema, pustules/papules, telangiectasia, and/or phymatous changes.[2] Based on these morphological changes, four major types of rosacea have been described: rhinophyma, erythematotelangiectatic rosacea, papulopustular rosacea, and ocular rosacea, with erythematotelangiectatic and papulopustular types most prevalent.[3] Rosacea is a fairly common condition, with a recent meta-analysis reporting a likely underestimated 5.46% global prevalence.[4] Conventional treatments for rosacea include topical and oral therapies, laser treatments, injections, and skincare/cosmetic modalities.[5] Treatments can also be tailored to specific types of rosacea.

In recent years, studies have implicated oxidative stress in the pathophysiology of rosacea, finding associations with inflammation, oxidative tissue damage, and vascular changes.[6] There has been an increasing amount of evidence suggesting that *Demodex* mites may be a trigger of this inflammatory cascade.[7] As a result of this oxidative pathogenesis, there has been increasing interest in evaluating the effects of using naturally occurring antioxidants as therapeutic agents for managing rosacea. Many studies have described the benefits of natural antioxidants in the treatment of rosacea, and our review intends to provide a resource that clinicians can use when counseling patients about adjunct options. In this review, we discuss therapeutic applications of grape seed extract (GSE), vitamin C, azelaic acid, and zinc, which have been studied for effects on reducing rosacea (Table 1). These remedies are of particular interest in recent years, as they have been increasingly used as ingredients in cosmeceuticals and discussed in the media.

GRAPE SEED EXTRACT

Grape seed extract (GSE) contains high amounts of polyphenols, including the ingredient resveratrol, which shows strong antioxidant properties.[8] Several applications of GSE in dermatology have been documented, including potentially reducing the risk for melanoma and helping to manage hyperpigmentation.[9,10] The literature evaluating the benefits of GSE for rosacea is limited, though early findings are promising. A study by Ferzli et al evaluated the effectiveness of combined resveratrol, green tea polyphenols, and caffeine on reducing facial redness in a cohort of 16 patients, finding improvement with continuous treatment for 6 weeks.[11] In the study, participants applied the antioxidant blend twice daily, and no adverse events were reported. Though these early results are promising, it is important to note that the literature is still limited by small samples and lacking comparisons with control subjects. Compared to other conditions, the current research for GSE in managing rosacea is sparse and requires further investigations. Nonetheless, GSE may be a promising remedy given its strong safety profile and well-documented antioxidant properties.

VITAMIN C

Vitamin C is a commonly used topical agent with anti-inflammatory and antioxidant properties that can mitigate the free radical production that occurs in rosacea.[12] It has been shown to have some efficacy in several other dermatologic conditions, such as hyperpigmentation and skin inflammation.[13] However, the literature investigating the effectiveness of treating rosacea with vitamin C is sparse, thus further research is required before firm conclusions can be made. Vitamin C is an interesting agent due to its collagen boosting and antioxidant properties, which can have a substantial role in protecting skin health.[14] A study

Table 1. Integrative treatments for rosacea

	Study Reference	Study Design	Description of Sample	Key Findings
Grape Seed Extract (GSE)				
	Ferzli et al (2013)	RCT	Individuals (N = 16) were evaluated for a decrease in facial redness after applying a topical containing resveratrol, green tea polyphenols, and caffeine	There was improvement in facial redness with continuous treatment for six weeks.
Vitamin C				
	Carlin et al (2001)	RCT	Individuals (N = 12) were given a 5% OTC vitamin C topical to use daily	Vitamin C was proved to be an effective treatment for rosacea, as 9 out of 12 participants demonstrated improvements.
Azelaic Acid				
	Draelos et al (2015)	RCT	All subjects presenting with papulopustular rosacea (N = 961) received either 1) 15% azelaic acid or 2) vehicle treatment	Azelaic acid foam was more effective with a success rate of 32%, compared to the vehicle treatment with a success rate of 23.5% ($p < 0.001$).
	Elewski et al (2003)	RCT	All subjects presenting with papulopustular rosacea (N = 251) received either 1) 15% azelaic acid or 2) 0.75% metronidazole gel	Azelaic acid was more effective than metronidazole in reducing lesion count ($p = 0.003$) and average percent decrease in inflammatory lesions ($p < 0.001$).
Zinc				
	Sharquie et al (2006)	RCT	Patients (N = 25) were randomized into two groups. Group A initially received 100 mg oral zinc sulfate and then switched to the placebo after 3 months. Group B initially received the placebo pill and were switched to 100 mg oral zinc sulfate after 3 months.	Group A saw improvement within the first 3 months ($p < 0.001$) until they switched to the placebo pill, where their severity score began to rise but remained significantly lower than the levels before therapy. Group B had no noticeable change in their severity score for the first 3 months but began to decrease after the fourth month when they shifted to the zinc sulfate treatment ($p < 0.01$)
	Sharquie et al (2014)	RCT	Patients (N = 22) were split into two groups, receiving either 1) 2% tea lotion or 2) 5% zinc solution twice daily.	Patients who received 2% tea lotion did not see an effective treatment in their rosacea ($p = 0.1$), whereas patients who received the zinc solution did see an improvement ($p = 0.00003$).
Turmeric				
	Vaughn et al (2019)	RCT	Individuals (N = 33) were randomly divided into 3 different groups and were either given a placebo tablet, 500 mg of turmeric, or a 500 mg turmeric polyherbal supplement.	There was no change in facial redness for the groups who received the placebo pill ($p = 0.27$) or the group who received solely turmeric ($p = 0.15$). Individuals who received the polyherbal treatment had a 40% decrease in redness compared to baseline ($p = 0.03$).

by Carlin et al used an observer blind and placebo-controlled approach in using a 5% topical preparation of vitamin C daily. A total of 12 patients participated in the study and results demonstrated that vitamin C was an effective treatment for rosacea, as 9 out of 12 patients showed noticeable improvements.[15]

AZELAIC ACID

Azelaic acid is an effective treatment for a broad range of cutaneous disorders due to its ability to inhibit follicular keratinization and epidermal melanogenesis.[16] In addition, azelaic acid is thought to inhibit interleukin-1, interleukin-6, and tumor necrosis factor, which all contribute to reactive oxygen species formation.[17] A potential mechanistic explanation for azelaic acid's effectiveness for treating

rosacea is its potent antioxidant effects, which have been shown through *in-vitro* models.[18]

A RCT performed by Draelos et al consisted of 961 patients with papulopustular rosacea who were given either 15% azelaic acid foam to use twice daily for 12 weeks or vehicle treatment.[19] Efficacy was measured by numerical change in inflammatory lesion count. Azelaic acid foam was more effective with a success rate of 32%, compared to the vehicle treatment with a success rate of 23.5% ($p < 0.001$). A study by Elewski et al compared the effects of two topical treatments, 15% azelaic acid gel and 0.75% metronidazole gel, on patients with papulopustular rosacea with persistent erythema and telangiectasia.[20] A total of 251 patients participated in this study and were randomized to either of the two treatments. They were instructed to use it twice daily. The study found that azelaic acid was more effective than metronidazole in reducing lesion count ($p = 0.003$) and average percent decrease in inflammatory lesions ($p < 0.001$). Azelaic acid was also more effective in treating erythema, with a 56% improvement rate for these patients, compared to a 42% improvement in patients treated with metronidazole gel ($p = 0.02$). Several studies in the literature suggest that azelaic acid effectively decreases free radical production, leading to improvements in rosacea patients. In 2002, azelaic acid 15% gel was approved for the topical treatment of mild to moderate rosacea.[21] This 15% gel was found to be well tolerated with a generally high efficacy in rosacea patients. In sum, azelaic acid is as an effective therapeutic possibly due to its antioxidant properties.

ZINC

Zinc has been used as a therapeutic topical for centuries for its photoprotective effects and soothing properties.[22] Over the years, it has been a notable treatment option for several dermatologic conditions including inflammatory dermatoses, such as acne vulgaris and rosacea.[22] Topical zinc pyrithione has also been used to treat seborrheic dermatitis, which is often a comorbidity in rosacea patients.[23] The use of zinc stems from its potent antioxidant properties. These properties stem from several proposed mechanisms. These include NADPH oxidase inhibition, inducible nitric acid synthase (iNos) inhibition, and upregulation of antioxidant factors (nuclear factor erythroid 2-related factor 2, catalase, 8-glutathione, and superoxide dismutase).[24]

A total of 25 patients were included in a study by Sharquie et al that observed the effects of oral zinc sulfate as a potential treatment for rosacea.[25] Prior to treatment, each patient was given a severity score, which served as a measure of progression of their disease and would be the key indicator for the success of the treatment. Patients were randomly given either 100 mg of zinc sulfate or placebo capsules three times daily. After 3 months of treatment, patients who were initially given the 100 mg zinc sulfate crossed over to the placebo (group A) and vice versa for the placebo patients (group B). Initially, patients in group A had a severity score that ranged between 5 and 11 with a mean ± SD of 8 ± 2.0. Their mean severity score began to decrease after the first month of treatment (5.7, 3.4, and 1.6 for the first, second, and third months, respectively; $p < 0.01$). After they shifted to the placebo treatment, their score began to rise again but remained significantly lower than the levels before therapy (1.9, 1.8, and 2.6 for the fourth, fifth, and sixth months respectively). The severity score for group B ranged between 5 and 9 with a mean ± SD of 7 ± 1.3. Their mean remained high for the first three months of therapy (7.3, 7.4, and 7.6 for the first, second, and third months, respectively), but began to decrease after the fourth month when they shifted to the zinc sulfate treatment (5.9, 3.9, and 1.9 for the fourth, fifth, and sixth months, respectively; $p < 0.01$). Only three patients complained of side effects, all with mild gastric upset.

Zinc has also been evaluated topically. A study by Sharquie et al included 22 individuals with rosacea which compared the efficacy of 2% tea lotion with a 5% zinc sulfate solution in treating acne rosacea.[26] Individuals were randomly divided into group A, which was instructed to use 2% tea lotion twice daily, and group B, which was instructed to use 5% zinc sulfate solution twice daily. Chemicals such as tannins in tea (mainly catechine) have an antibacterial effect, and previous studies have shown effectiveness in treating acne vulgaris and impetigo. Patients were evaluated every two weeks by comparing their disease severity score before and after treatment. Results demonstrated that patients in group A who initially had a mean ± SD severity score 6.1 ± 1.8 decreased to 4.2 ± 2.6 after treatment, which was not statistically significant ($p = 0.1$). Patients in group A who initially had a mean ± SD severity score 7.4 ± 1.9 decreased to 2.9 ± 1.9 after treatment, which was statistically significant ($p = 0.00003$). The majority of patients did not experience any side effects. In the tea lotion group, one patient complained of a burning sensation while another complained of itchiness. In the zinc sulfate group, two patients experienced a burning sensation, while one experienced itching. No patients needed to cease treatment.

Ultimately, multiple studies have demonstrated favorable effects of zinc in treating rosacea in both topical and oral formulations.

TURMERIC

Though the literature supporting the efficacy of turmeric is sparse, turmeric is known to reduce inflammation, hyperpigmentation, and erythema in psoriasis.[27,28] It is beneficial in wound healing, prevention of damage from ultraviolet B light (length range 280 – 315 nanometers), and may play a role in decreasing facial redness or rosacea.[29] Curcumin is a polyphenol and is the most biologically active component of turmeric. Of note, polyphenols in turmeric drive its volatile, aromatic, and flavonoid properties, making it commonly used for culinary purposes.[30] Curcumin can be obtained from *Curcuma longa* (the genus and species name for turmeric) rhizomes and has several antioxidant, anti-inflammatory, antifungal, and anticancer properties. Rhizomes are horizontal stems that continuously grow underground.[31]

A study by Vaughn et al studied the effects of turmeric polyherbal dietary supplementation on facial redness in

33 individuals.[32] Individuals were randomly divided into three groups and were either given a placebo tablet, 500 mg of turmeric, or a 500 mg turmeric polyherbal supplement which contained several natural herbs including *C. longa* (turmeric) root, *H. indicus* (anantamul) root, *R. cordifolia* (manjistha) root, *A. indica* (neem) leaf, *C. asiatica* (brahmi/gotu kola) leaf, *T. cordifolia* (guduchi) stem, *P. amarus* (bhumyamalaki) herb, *P. emblica* (amalaki) fruit and *G. glabra* (licorice) root. After four weeks, the polyherbal combination group had a 40% decrease in redness compared to baseline ($p = 0.03$). There was no change in facial redness for either the group who received the placebo pill ($p = 0.27$) or the group who received solely turmeric ($p = 0.15$).

Turmeric was not sufficient in effectively decreasing facial redness in this study, with such limited evidence, it is difficult to make a definitive statement on the effects of turmeric on rosacea treatment.

CONCLUSION

Naturally occurring antioxidants are readily available and familiar for patients, carrying little risk for adverse events and improving satisfaction. Though this article is limited in that it was not performed via an all-inclusive systematic search, we illustrate that research has begun to support the use of these natural products as adjunct options when treating rosacea pathophysiology. Patients seeking complementary options for rosacea can be encouraged to use the natural antioxidants such as grape seed extract (GSE), vitamin C, azelaic acid, and zinc.

CONFLICTS OF INTEREST

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