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 ORIGINAL ARTICLE

A Novel Systems-Wide Approach in Addressing Acne With a Multi-Targeting Nutraceutical

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ABSTRACT

Acne vulgaris (AV) is one of the top concerns dermatologists encounter from women. Until now, therapies addressing AV have largely centered around, and have been successful at, targeting the pathophysiological mechanisms that occur at the pilosebaceous unit: sebum hypersecretion, follicular keratinization, over-proliferation of *Cutibacterium acnes*, and a localized immune response. In addition to these, there is good evidence to suggest that other systemic drivers of a generalized inflammatory response may contribute to the development or exacerbation of acne and that addressing these underlying factors may open more opportunities for developing effective treatments. These include psycho-emotional stress, diet and metabolism, hormonal fluctuations, skin and gut microbiome, oxidative stress, and immune response. While there is accumulating evidence that vitamins, minerals, and botanicals may mitigate some of the pro-inflammatory effects from the activation of these underlying systems, their use and recommendations are limited by a lack of quality efficacy and safety evidence. Here, we present the current evidence for the use of individual supplements in addressing the 6 systemic underlying drivers of AV. We also present a clinical study on the safety and efficacy of a nutraceutical combining many of these ingredients in the management of AV in men and women.

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INTRODUCTION

Acne vulgaris (AV) is the number one skincare concern of women ages 18-50 years and is in the top 3 complaints dermatologists see in their office, with the prevalence increasing across the globe.[1,2] As patients and providers search for effective treatments for such a large portion of the population, the market for treatments is also growing and is expected to increase by 5% compounded annual growth rate by 2030.[1]

In the pursuit of finding effective therapeutics for AV, conventional medicine has characterized the correlation of pathophysiology of the Pilosebaceous Unit (PSU) and AV lesion formation with 4 mechanisms: excess sebum production, follicular keratinization causing an obstructed follicular orifice, and the over-proliferation of *Cutibacterium acnes*, triggering an immune response. With this understanding, options for the management of AV targeting the pathophysiology at the PSU have been developed, from prescription and over-the-counter (OTC) medications to at-home devices.[3,4] Current treatment regimens often include azelaic acid, benzoyl peroxide, or retinoids, which all target follicular keratinization, *C. acnes* proliferation, and inflammation. Oral antibiotics, isotretinoin, hormone therapy, or a combination target all 4 of the underlying mechanisms occurring at the AV lesion site.[5]

While benzoyl peroxide, retinoids, and antibiotics are known to be effective in treating AV, some of these therapeutics are limited in their use as more attention is being paid to the secondary effects associated with their use. For example, dermatologists prescribe antibiotics almost twice as much as providers of other specialties, with strong implications for the rise of antibiotic resistance.[6] Additionally, approximately 37% of acne patients discontinue using acne products because of the side effects.[2]

A growing trend in acne management is for a more integrative, systemic approach, driven by both patients and providers. In addition to the local inflammation at the PSU, there is now a growing body of evidence that suggests that AV may be driven by underlying systemic, immune-inflammatory pathways. Some purported mechanisms include: Psycho-emotional stress leads to a neuroendocrine response and the release of inflammatory cytokines in the skin; Diet and metabolism, such as high glycemic diets, insulin, and aberrant vitamin levels are associated with inflammatory pathways in the skin; Dysbiosis of the gut and skin microbiome can lead to the overgrowth of pathogenic microbes, triggering an immune response; Excess androgens and hormonal fluctuations may stimulate sebocytes and PSU inflammation; Oxidative stress triggered by internal

and external mechanisms causes cellular damage; Finally, dysregulated immune function, oftentimes downstream of the other intertwined systems, is a direct link to the inflammatory response at the PSU. A recent review by Del Rosso et al[71] discusses the current clinical data supporting these as the systemic patient-centric approach to AV.

Natural compounds and dietary supplements, including nutraceuticals used in complementary and alternative medicine, are a growing trend in wellness and beauty and may offer an expanded approach to the treatment and management of AV beyond conventional medicines addressing the pathophysiology only at the PSU.[2,4] For example, vitamin A was one of the first vitamins to be recommended for its role in treating acne and is now the basis for the development of tretinoin and isotretinoin, which are powerful AV treatments.[7] We can also see that treating the systemic drivers of hair thinning has found success, as supplements that provide whole-body support for daily stressors from metabolism, lifestyle, hormones, and others have repeatedly been shown to improve hair thinning over time in different populations.[8-11]

But, while supplements are regulated by the US Food and Drug Administration, they are not subjected to the same standards as drugs, and oftentimes, there is limited data from well-designed clinical studies. Very recently, a systematic review in *JAMA Dermatology* looking for evidence for oral nutraceuticals in the treatment of AV identified 2582 abstracts of which only 42 met their criteria (a total of 3346 participants).[12] Still, the review presented several studies showing encouraging data for the safety and effectiveness of oral nutraceuticals for treating AV and noted vitamin D, green tea extract, probiotics, and several others as having fair- to good-quality studies in this space.[12] Furthermore, fish oil, probiotics, and oral zinc have been studied for their role in treating AV, yet convincing data regarding the safety and efficacy of these agents is still too limited to be recommended in the AAD Guidelines of Care for Management of Acne.[4] Because of this, their use and recommendation for addressing AV is limited.

In this article, we review clinical evidence for various botanicals, vitamins, and minerals to address the systemic root causes of AV (stress, diet and metabolism, hormones, skin and gut microbiome dysbiosis, oxidative stress, and immune response). Although the severity of AV in these studies is not always noted, the type of acne is reported when available. We also present the promising results of a 12-week clinical study using a supplement containing 20 botanicals, vitamins, and minerals supported by evidence to address non-cystic acne or improve skin health. Broadening the scope of therapeutics to include a systemic approach using standardized, effective ingredients could offer a more comprehensive approach to AV management. To continue pushing the field of dermatology forward, we need to bridge the gap between the clinical evidence suggesting systemic drivers of AV and the clinical effectiveness of dietary supplements and botanicals to address those targets. When we do that, we may be able to improve clinical outcomes of AV patients, whether that is used in conjunction with conventional treatments, decreasing the dose or treatment time, or offering more natural solutions for patients who prefer so.

Addressing the Stress Response in the Skin

Clinically, higher reported stress levels have been associated with an increased acne grade in adult women.[13,14] While these data confirm the anecdotal reports of the impact of systemic stress on acne in adult females, there is a lack of therapeutics available to address psycho-emotional stress in the acne patient. Oftentimes suggestions to decrease stress can focus on a lifestyle change, for example, meditation, yoga, and exercise can be recommended to reduce stress that contributes to adult acne.[15]

Alternative medicinal practices have characterized a few botanicals that have been used to manage stress with purported physiological mechanisms. Ashwagandha, a shrub found in Asia and Africa, has now become popular as an "adaptogen," and may prevent the detrimental fluctuations of cortisol and other stress hormones released during a generalized stress response.[16] The natural ayurvedic Holy Basil (*Ocimum tenuiflorum*) has also been used in traditional medicine to combat stress.[17] In a double-blind, placebo-controlled study, adult participants who received Holy Basil showed a significant decrease in the self-reported perceived stress scale as well as a decrease in salivary and hair cortisol levels.[17,18] On a mechanistic level, pre-clinical and clinical studies also indicate additional potential benefits including its antioxidant, analgesic, and anti-inflammatory properties.[19,20] Its medicinal properties are attributed to its biochemically active components such as eugenol, carvacol, and rosmarinic acid.[17] In a recent systematic review, Holy Basil was found to be therapeutically associated with improving psychological, physiological, metabolic, and immunological impacts of lifestyle-related chronic disease.[20] The improvement across these domains is attributed to Holy Basil's anti-inflammatory effects, making it a candidate that may also be useful in targeting the underlying stress-induced inflammation reported in patients with AV.[20]

Diet and Metabolism

Sugar consumption and insulin fluctuation have been directly implicated in the development of AV.[4,21] As such, AV management also includes recommendations for consuming a low glycemic diet and maintaining balanced blood insulin levels. Studies suggest that the anti-diabetic medication metformin that targets gluconeogenesis improves AV in women with PCOS purportedly by reducing hyperinsulinism and the resulting ovarian hyperandrogenism.[22] It has also been suggested that

men with metabolic syndrome or insulin resistance with AV may also benefit from metformin treatment.[23] Beyond this, there are traditional botanicals that have been shown to help with balancing the negative effects of glucose and insulin fluctuations, such as berberine and ginger, which also may improve clinical manifestations of AV.

Berberine (*Berberis aristate*, Indian barberry) is a botanical that has been used in Chinese traditional medicine for hypercholesterolemia, diabetes type 2, and to fight infections.[24] Recent research suggests that it does so in part by improving blood glucose and insulin sensitivity through direct effects on LDL receptors and glucose absorption and uptake.[25-27] Berberine is now being tested for the management of dyslipidemia, diabetes, and obesity.[25-27] In fact, the effects of berberine on plasma lipids are recognized in The European guidelines for the management of dyslipidemias.[28] Now, evidence-based studies have linked potential therapeutically beneficial properties of berberine in AV patients. A 2002 comparative study of a tablet containing berberine vs minocycline in acne patients saw no difference between the 2 groups.[29] Another study in PCOS women with moderate acne reported a 61% decrease in Global Acne Grading System (GAGS) and 71% decrease in Cardiff Acne Disability Index (CADI).[24] Moreover, the relatively minor side effect profile of berberine has seen success when used in patient populations such as those with PCOS or dyslipidemia, where long-term modern therapies were not tolerated.[24] In this sense, berberine could provide a powerful tool against a novel target for patients with AV.

Ginger (*Zingier officinale*), has also been used in traditional medicine for its numerous benefits not only for addressing metabolic disorders, but also for its anti-inflammatory and anti-oxidative properties.[30,31] A meta-analysis examining the benefits of ginger on type II diabetes and the associated hyperglycemia found that HbA1c levels and fasting serum glucose levels improved with the consumption of ginger.[32] On a larger scale, the benefits of ginger were studied in a meta-analysis including patients with type 2 diabetes, non-alcoholic fatty liver disease, and osteoarthritis. They found that the intake of ginger significantly decreased circulating levels of CRP and tumor necrosis factor-alpha (TNF-α).[30]

Another important aspect of the patient's metabolic profile is their consumption of key vitamins and minerals, and as dermatologists, we have been trained to assess this. In patients with AV, low levels of vitamin A, D, and selenium have been reported and there is growing evidence that once corrected, AV may improve.[33-35] Placebo-controlled clinical studies show that supplementing with zinc significantly decreases inflammatory acne scores and improves AV severity in patients.[36,37] Niacinamide (vitamin B3) is a key precursor to the coenzymes NAD/NADP/NADH/NADPH, critical for reduction-oxidation reactions throughout the body.[38] Niacinamide has been shown to have a wide range of purported benefits in the skin: it has antioxidant effects, improves epidermal barrier function, increases dermal collagen and protein production, and reduces hyperpigmentation.[39] Specific to AV, in a formula combined with other ingredients including azelaic acid, zinc, copper, pyridoxine, and folic acid; ingestible niacinamide has been shown to reduce inflammatory papules.[40] Indications suggest that vitamin D may be a potent immune modulator with endocrine, paracrine, and autocrine functions.[38] Finally, women with PCOS who received selenium in a double-blind, placebo-controlled trial had significantly decreased DHEA levels.[41] All of this evidence suggests there may be an overlap of underlying whole-body drivers of AV and a necessity to balance them to manage AV and promote general skin health.

Gut and Skin Microbiome

Antibiotics are a mainstay of acne treatment due to the role of *C. acnes* in the pathogenesis of AV.[42] Both oral and topical antibiotics are commonly prescribed, although short-course therapy is now favored due to the potential for developing antibiotic resistance.[43] Along with this, research suggests that the gut microbiome in patients with AV may be less diverse and has a higher ratio of *Bacteroides* to Firmicutes.[42,44] The gut microbiome has been shown to interact with the nutrient-sensitive kinase mammalian target of rapamycin (mTORC), known to play a role in the pathogenesis of AV.[45] Oral antibiotics also contribute to gut dysbiosis in patients with moderate-to-severe AV.[42,46]

Along the same lines, using milk cultures with bacteria topically to treat AV dates back to the 1930s, showing the use of natural remedies to manage the microbiome and thus the underlying pathogenesis of AV.[47] Current findings now indicate that improved biodiversity of the skin and gut microbiome is essential for epithelial health.[48,49] Clinical studies suggest that supplementing with probiotics may improve symptoms of AV, in part by decreasing sebum production, which could reduce follicular colonization of *C. acnes* and the associated inflammation.[47] It also may have immunomodulatory properties through the inhibition of cytokines in epithelial cells and keratinocytes.[47] Supplementing with commensals has also been suggested to aid in the remediation of leaky gut, leading to an improved inflammatory profile systemically.[50] The daily intake of the heat-killed postbiotic L-137 has been linked to improved skin parameters such as improved TEWL and improved dermatology life quality index in participants with dry skin.[51]

The gut microbes may also interact directly with the intestinal lumen cells by promoting immune responses. Short-chain fatty acids (SCFA) such as butyrate, are synthesized and released in the colon by bacterial fermentation of starches and fibers.[52] Clinical data suggests that patients with AV have an

underrepresentation of *Bifidobacterium* and *Butyricicoccus*, which are primary producers of butyrate.[50] Research suggests that butyrate may play a key role in improving the epithelial defense barrier, improving oxidative status, and relieving mucosal inflammation.[53] It does so in part by providing energy to the gastrointestinal cells.[52] Preclinical research indicates that butyrate may have a pro-apoptotic effect on the cell cycle, as well as effects on proliferation and differentiation.[54] This is believed to be the underlying mechanism in its beneficial effects on hyperproliferative skin diseases such as psoriasis.[54] In addition to directly providing energy and cell cycle control, butyrate may also activate regulatory T cells, which could be a connection to its anti-inflammatory properties.[54]

Hormones

Balancing androgen levels is used to treat AV in the clinic. Combined oral contraceptives mitigate the effect of hormonal fluctuation, improving AV in female patients.[4] Spironolactone is a potassium-sparing diuretic with anti-androgenic properties.[55] It is now used widely to treat female patients with AV and is considered an alternative to antibiotic therapy.[4] Spironolactone is used at doses of 50-100mg/day for treating female patients with mild-to-severe AV but is contraindicated in patients who are pregnant or trying to conceive.[55,56] While efficacious, these treatments are irrelevant to at least half the population or may come with unwanted side effects.[4]

Alternatively, botanicals have been used to mitigate mild effects of excess androgens in conditions such as menopause and PCOS. Maca (*Lepidium meyenii*), for example, is a Peruvian root used in high altitudes to maintain health and energy and address female-specific hormonal imbalances such as infertility and menstrual irregularities.[57] In a double-blind, randomized, placebo-controlled study of early post-menopausal women, the oral intake of Maca tablets was significantly correlated to an increase in E2 production and suppression of FSH and LH.[57] It also was linked to an increase in High Density Lipoprotein (HDL) levels and alleviated the frequency and severity of reported menopausal symptoms such as hot flushes and night sweats.[57] Maca has also been associated with lower serum IL-6 levels and mitigated antidepressant-induced sexual dysfunction.[58,59] All of this suggests that Maca could be a useful botanical supplement for addressing the underlying hormonal component of AV.

Selenium is also now being explored for its role in AV along with its androgen-modulating properties. Selenium levels in patients with AV have been reported as lower than in the general population.[60] In a double-blind placebo-controlled study, women with PCOS who supplemented with selenium for 8 weeks showed significant improvement in AV.[41] The study also noted a decrease in DHEA-S levels, an androgen that has been shown to be elevated in patients with AV.[41] The oral intake of selenium was also associated with a significant decrease in C-reactive protein (CRP) and plasma malondialdehyde (MDA) levels, both markers for oxidative stress.[41] When taking a patient-centric view, these findings suggest a link between decreased inflammation, oxidative stress, and AV improvement.

Oxidative Stress

While oxidative stress has not been specifically targeted by modern medicine in the clinic, many of the natural anti-aging phytochemicals with purported benefits in the skin in use today contain anti-oxidative properties. Lycopene, for example, in high concentrations in tomatoes, has been shown to inhibit oxidative markers that are generated in the skin during exposure to ultraviolet (UV) A and UVB.[61] The oral intake of olive oil, long used for its supposed beneficial effects on the skin, was linked to a dose-dependent increase in HDL and the intracellular antioxidant glutathione peroxidase (GSH-Px), and a dose-dependent decrease in plasma oxidized LDL and other oxidized DNA and poly-unsaturated fatty acid (PUFA) markers.[62] It was also associated with an increase in plasma concentrations of antioxidants such as tyrosol, hydroxytyrosol, and 3-O-methylhydroxytyrosol (MHT), a biological metabolite of hydroxytyrosol.[62] In addition, a systematic review and meta-analysis concluded that ginger supplementation significantly reduced MDA levels as well as GSH-Px, both markers for oxidative stress.[31]

Sicilian orange, also known as blood oranges or Red Orange (*Citrus sinensis*, varieties *Moro, Tarocco, and Sanguinello*) has demonstrated high levels of antioxidative properties. A significant crop grown and exported in high-UV regions such as Italy and Egypt, blood oranges and their peels are rich sources of vitamin C.[63,64] Their consumption for anti-aging properties is now being explored. An extract of these Sicilian Red Oranges has been shown to contain high levels of antioxidants such as anthocyanins, hydroxycinnamic acids, flavanones, and ascorbic acid.[63] A recent study showed that consumption of this complex decreased UV-induced skin redness, in part by increasing the total antioxidant capacity of the skin.[63] MDA levels were significantly lower in the active group, indicating a decrease in lipoperoxide levels due to UV stimulation.[63] With the strong indications for UV damage and its role in AV development and epidermal integrity, antioxidants may be useful in the mitigation of this damage, which could improve skin health.

Immune Function

Considering that the systemic drivers discussed here and in Del Rosso et al[71] have been linked to pathways that may drive generalized immuno-inflammatory activation, targeting and attenuating components of an irregular immune system could improve AV outcomes. Curcumin, the golden component of turmeric, is widely known for its use in Asian and Indian cuisine. It has also been used for centuries for its anti-inflammatory properties and is now being investigated for its

use in inflammatory bowel disease, colon cancer, psoriasis, rheumatoid arthritis, and a multitude of other inflammatory conditions.[65,66] New insights into molecular pathophysiology now indicate that curcumin may attenuate the generalized inflammatory response in part by lowering circulating levels of TNF-α and CRP, key inflammatory mediators released during injury or tissue damage.[65] In fact, TNF-α inhibitors used to treat other inflammatory diseases are sometimes used off-label to treat cases of severe AV that are not responsive to other treatments.[67] Curcumin may also prevent the onset and development of an inflammatory response by suppressing the transcription factor NF-kB, a key regulator of genes associated with generalized inflammation.[68]

Indirectly, curcumin mitigates a generalized inflammatory response through its protective effects as an antioxidant. Curcumin's polyphenolic structure acts as a free radical scavenger, which could improve antioxidant capacity in the skin to mitigate damage by UV and environmental assaults.[68] It has also been shown to increase the cellular antioxidant GSH, which would prevent ROS-induced tissue damage.[68] Studies specifically in fibroblasts and keratinocytes have shown increased protective effects of curcumin against H2O2.[68]

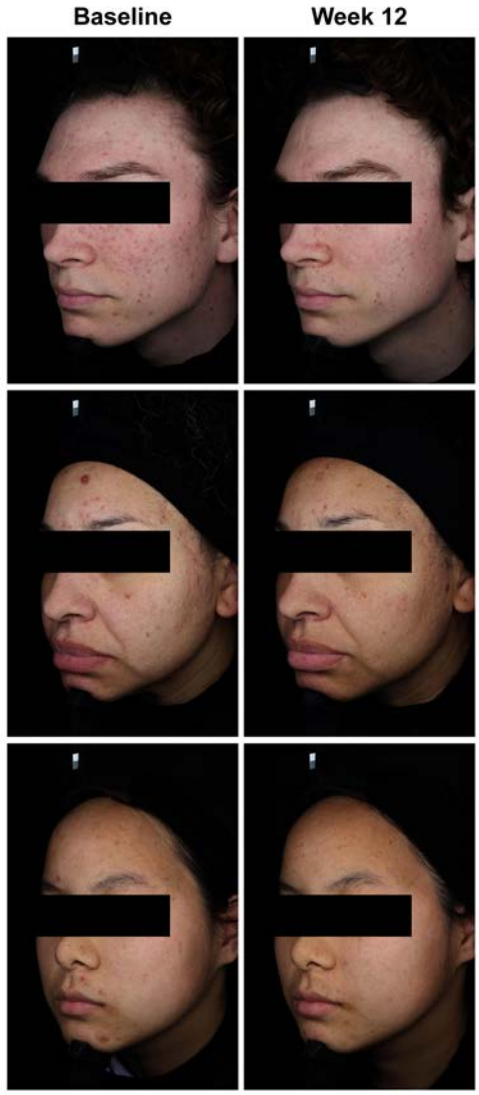
Important in AV, curcumin has also been shown to have anti-microbial properties against opportunistic microbes such as *S. epidermis* and *C. acnes*. With this, curcumin has been linked to the suppression of bacterial proliferation and the formation of biofilms by decreasing adhesion molecules of the microbes.[68] Knowing that antibiotics have proven successful in the treatment of AV, these antimicrobial properties could also be a tool to improve outcomes in patients with AV.

Considering curcumin's compelling therapeutic profile, much focus has been on improving its limited bioavailability in its natural form. Patented biotechnology has found that reconstituting 95% standardized curcumin in non-curcuminoid oil from turmeric improves bioavailability by almost 700% compared to curcumin alone.[69] With this, the therapeutic potential of curcumin described for centuries can be incorporated into dietary intake.

Clinical Support for the Combination of a Standardized Acne Supplement

As reviewed here, several ingredients have been clincially studied to improve some of the underlying root causes of acne on their own. One would expect, then, that combining varying amounts of key ingredients could theoretically have better clinical results compared to single target ingredients that have thus been evaluated in patients with acne. A novel nutraceutical was recently formulated to include key ingredients to address multiple systems-wide root causes of acne (Table 1). This combination nutraceutical could potentially enable less usage of any one specific ingredient and have the benefit of the multi-faceted approach.

FIGURE 1. Cross polarized images of baseline and week 12 timepoints in 3 participants with mild-to-moderate acne.



The Standardized Nutraceutical was evaluated in a proof-of-concept study conducted in 51 adults with non-cystic acne. The study was approved by an Institutional Review Board (Advarra IRB, Columbia, MD) and conducted in accordance with accepted standards for Good Clinical Practices. All participants provided written informed consent prior to participating, consistent with the requirements in 21 Code of Federal Regulations (CFR) 50.25. This was a 12-week single-arm prospective study for women and men aged 18 to 50 years with facial acne ranging from mild to severe, excluding cystic acne. Participants discontinued all acne medications and topicals prior to the start

TABLE 1.

Selection of Key Ingredients in a Standardized Nutraceutical for Skin		
Synergen Skin Complex	**Additional Key Ingredients**	**Nutrient Supportive Ingredients**
Holy Basil	Olive Extract	Vitamin A
Maca	Konjac Root	Vitamin B3 (Niacinamide), B5 (Pantothenic Acid), B9 (Folate)
Curcumin	Tributyrin	Vitamin C
Berberine	Probiotic (B. subtilis DE111®)	Vitamin D3
Postbiotic (HK *L. Plantarum*)	Lycopene	Selenium
Sicilian Orange	Ginger Extract	Zinc

TABLE 2.

Improvements in Acne and Skin Parameters				
Measurement	**Baseline**	**Week 12**	**% of Subjects Improved**	***P* value**
IGA of Acne Severity	2.5	1.7	85	<0.001*
Lesion Count				
Inflammatory	8.0	5.2	69	<0.001*
Non-inflammatory	19.4	10.3	87	<0.001*
Bioinstrumentation				
Sebumeter	158.1	121.6	72	0.002+
Corneometer	35.0	42.8	74	0.002+
Tewameter	18.6	19.9	41	0.361+

Mean values reported. *Determined through Wilcoxon-signed rank test. +Determined through paired t-test. Significance set at *P* values <0.05

of the study. Clinical assessments at baseline and weeks 4, 8, and 12 included Investigator Global Assessment (IGA) of acne severity, inflammatory and non-inflammatory lesion counts, and clinical grading of skin health, including post-inflammatory hyperpigmentation/erythema (PIH/PIE). Bioinstrumentation (corneometer, tewameter, sebumeter) and subjective questionnaires on perception of efficacy were also completed at each visit.

Significant and progressive improvements were seen in acne parameters, shown in Table 2. Specifically, IGA of acne severity showed a decrease of 30% from baseline to week 12 (baseline: 2.47 ± 0.60, week 12: 1.73 ± 0.71) . In addition, IGA scores of acne severity improved in 85% of the participants by week 12. Average lesion counts also significantly decreased throughout the study, with a 35% decrease in inflammatory lesion counts and 47% decrease in non-inflammatory lesion counts (Table 2). Overall, clinical grading of skin quality parameters progressively and significantly improved throughout the study. Notably, post-inflammatory hyperpigmentation/ post-inflammatory erythema (PIH/PIE) parameters improved in nearly 80% of participants by week 12. Skin hydration as measured by the corneometer also improved in 74% of subjects. Sebumeter measurements improved significantly with a decrease of 25% as early as week 4 and remained lower than baseline throughout the study. Participants also reported improvements at 12 weeks, including "clearer skin," "less breakouts," "less oily skin," and that their "acne had improved" (87%). Although preliminary, these results are promising and warrant further research. A randomized, placebo-controlled trial is currently underway.

CONCLUSION

Conventional treatments, while shown to be clinically effective in decreasing the severity of AV, are becoming more challenging to access with insurance companies often denying prescription medications for AV. In addition, side effects, including antibiotic resistance, photosensitivity, and pregnancy contraindications, are of concern to many patients considering oral therapies for AV. These barriers to treatment are a significant challenge for AV patients, leading many to search for alternatives that are safe and effective. Additionally, therapeutic options that reduce the need for topical and/or oral antibiotic therapy for AV are an important focus, as bacterial resistance to antibiotics is a clinically relevant concern both in the United States and globally.

Dermatologists are also recommending an increasing number of OTC treatment options as they are more easily accessible and affordable for patients. While effective, OTC treatments still target the conventional, local AV pathophysiology described as 4 major pillars at the site of the acne lesion. There is, however,

substantial support that whole-body factors such as stress, diet and nutrition, gut and skin microbiome, hormones, oxidative stress, and immune function contribute to a generalized, dysregulated immune-inflammatory response. This was discussed in a recent review from Del Rosso et al.[71] Now, the authors propose the consideration of therapeutics that have traditionally been used, and have clinical support, to address these systemic dysregulations on a patient-centric level.

Complementary and alternative medicine (CAM), such as nutraceuticals, have long been explored for their use in improving skin health, but the paucity of scientific evidence and lack of clinical data on the safety and efficacy have limited their recommendation for use in the clinic for AV. Now, scientific literature is bridging the gap with clinical evidence that provides support for a systemic, multi-targeting approach. The approach does not reject the established, effective therapeutics that are available to us, rather it proposes an expanded consideration using evidence-based studies to provide a more comprehensive approach to AV management. In this paper, we provided the current evidence suggesting that many botanicals, vitamins, and minerals may be available to address underlying drivers of AV that conventional medicines ignore.

When combined, these ingredients may have the potential to improve AV and skin health. A 12-week proof-of-concept study showed improvements in AV and skin parameters in adults with mild-to-severe AV. Although more studies are needed, these results offer insight into the potential benefits of nutraceuticals addressing underlying mechanisms that up to now, have gone largely unexplored. Addressing dysregulation that contributes to a generalized inflammatory response in a patient-centric manner may prove to be an important step in expanding our toolbox in providing more options for AV management and improving skin health.

DISCLOSURES

Dr Burgess is a clinical investigator for Nutraceutical Wellness LLC but has not received compensation or services for any aspect of the submitted work. Dr Gold is a consultant for Nutraceutical Wellness LLC and is paid for those services. Dr Farris is a paid advisor for Nutraceutical Wellness LLC. Dr Hazan and Dr Raymond are employees of Nutraceutical Wellness LLC.

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REFERENCES

1. Acne Treatment Market. Report FBI103361. Fortune Business Insights. Published July 2023. Accessed July 2023. https://www.fortunebusinessinsights.com/acne-treatment-market-103361
2. U.S. Acne Treatment Market. Report FBI106565. Fortune Business Insights. Published July 2023.
3. Fortune Business Insights. U.S. acne treatment market size, share & COVID-19 impact analysis, by product type (retinoids, antibiotics, isotretinoin, and others), by treatment modality (oral and topical), by age group (10 to 17, 18 to 44, 45 to 64, and 65 and above), by distribution channel (hospital pharmacies and retail pharmacies), and country forecast, 2023-2030. https://www.fortunebusinessinsights.com/u-s-acne-treatment-market-106565. Accessed Sept, 2023.
4. Hauk L. Acne vulgaris: treatment guidelines from the AAD. *Am Fam Physician.* 2017;95(11):740-741.
5. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J *Am Acad Dermatol.* 2016;74(5):945-73 e33. doi:10.1016/j.jaad.2015.12.037
6. Baldwin H, Farberg A, Frey C, et al. Unmet needs in the management of acne vulgaris: a consensus statement. *J Drugs Dermatol.* 2023;22(6):582-587. doi:10.36849/JDD.7587
7. Graber EM. Treating acne with the tetracycline class of antibiotics: Areview. *Dermatological Reviews.* 2021;2:321-330. doi:10.1002/der2.49
8. Hartmann D, Bollag W. Historical aspects of the oral use of retinoids in acne. *J Dermatol. 1*993;20(11):674-8. doi:10.1111/j.1346-8138.1993.tb01362.x
9. Ablon G, Kogan S, Raymond I. A long-term study of the safety and efficacy of a nutraceutical supplement for promoting hair growth in perimenopausal, menopausal, and postmenopausal women. *J Drugs Dermatol.* 2022;21(7):783. doi:10.36849/JDD.776
10. Stephens TJ, Berkowitz S, Marshall T, et al. A prospective six-month single-blind study evaluating changes in hair growth and quality using a nutraceutical supplement in men and women of diverse ethnicities. *J Clin Aesthet Dermatol.* 2022;15(1):21-26.
11. Ablon G, Kogan S. A randomized, double-blind, placebo-controlled study of a nutraceutical supplement for promoting hair growth in perimenopausal, menopausal, and postmenopausal women with thinning hair. *J Drugs Dermatol.* 2021;20(1):55-61. doi:10.36849/JDD.5701
12. Ablon G, Kogan S. A six-month, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of a nutraceutical supplement for promoting hair growth in women with self-perceived thinning hair. *J Drugs Dermatol.* 2018;17(5):558-565.
13. Shields A, Ly S, Wafae B, et al. Safety and effectiveness of oral nutraceuticals for treating acne: a systematic review. *JAMA Dermatol.* 2023;doi:10.1001/jamadermatol.2023.3949
14. Dreno B, Thiboutot D, Layton AM, et al. Large-scale international study enhances understanding of an emerging acne population: adult females. *J Eur Acad Dermatol Venereol.* 2015;29(6):1096-106. doi:10.1111/jdv.12757
15. Zari S, Alrahmani D. The association between stress and acne among female medical students in Jeddah, Saudi Arabia. *Clin Cosmet Investig Dermatol.* 2017;10:503-506. doi:10.2147/CCID.S148499
16. Shenefelt PD. Mindfulness-based cognitive hypnotherapy and skin disorders. *Am J Clin Hypn.* 2018;61(1):34-44. doi:10.1080/00029157.2017.1419457
17. Lopresti AL, Smith SJ, Malvi H, et al. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study. *Medicine (Baltimore).* 2019;98(37):e17186. doi:10.1097/MD.0000000000017186
18. Lopresti AL, Smith SJ, Metse AP, et al. A randomized, double-blind, placebo-controlled trial investigating the effects of an Ocimum tenuiflorum (Holy Basil) extract (Holixer(TM)) on stress, mood, and sleep in adults experiencing stress. *Front Nutr.* 2022;9:965130. doi:10.3389/fnut.2022.965130
19. Sampath S, Mahapatra SC, Padhi MM, et al. Holy basil (Ocimum sanctum Linn.) leaf extract enhances specific cognitive parameters in healthy adult volunteers: A placebo controlled study. *Indian J Physiol Pharmacol.* 2015;59(1):69-77.
20. Singh S, Taneja M, Majumdar DK. Biological activities of Ocimum sanctum L. fixed oil–an overview. Indian *J Exp Biol.* 2007;45(5):403-12.
21. Jamshidi N, Cohen MM. The clinical efficacy and safety of tulsi in humans: a systematic review of the literature. *Evid Based Complement Alternat Med.* 2017;2017:9217567. doi:10.1155/2017/9217567
22. Baldwin H, Tan J. Effects of diet on acne and its response to treatment. *Am J Clin Dermatol.* 2021;22(1):55-65. doi:10.1007/s40257-020-00542-y
23. Sharma S, Mathur DK, Paliwal V, et al. Efficacy of metformin in the treatment of acne in women with polycystic ovarian syndrome: a newer approach to acne therapy. *J Clin Aesthet Dermatol.* 2019;12(5):34-38.
24. Andreadi A, Muscoli S, Tajmir R, et al. Insulin resistance and acne: the role of metformin as alternative therapy in men. *Pharmaceuticals (Basel).* 2022;16(1) doi:10.3390/ph16010027
25. Rondanelli M, Riva A, Petrangolini G, et al. Berberine phospholipid is an effective insulin sensitizer and improves metabolic and hormonal disorders in women with polycystic ovary syndrome: a one-group pretest-post-test explanatory study. *Nutrients.* 2021;13(10)doi:10.3390/nu13103665
26. Roshanravan B, Yousefizadeh S, Apaydin Yildirim B, et al. The effects of Berberis vulgaris L. and Berberis aristata L. in metabolic syndrome patients: a systematic and meta-analysis study. *Arch Physiol Biochem.* 2023;129(2):393-404. doi:10.1080/13813455.2020.1828482
27. Di Pierro F, Bellone I, Rapacioli G, et al. Clinical role of a fixed combination of standardized Berberis aristata and Silybum marianum extracts in diabetic and hypercholesterolemic patients intolerant to statins. *Diabetes Metab Syndr Obes.* 2015;8:89-96. doi:10.2147/DMSO.S78877
28. Poli A, Barbagallo CM, Cicero AFG, et al. Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper. *Pharmacol Res.* 2018;134:51-60. doi:10.1016/j.phrs.2018.05.015

29. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
30. He JM, Mu Q. The medicinal uses of the genus Mahonia in traditional Chinese medicine: An ethnopharmacological, phytochemical and pharmacological review. *J Ethnopharmacol.* 2015;175:668-83. doi:10.1016/j.jep.2015.09.013
31. Morvaridzadeh M, Fazelian S, Agah S, et al. Effect of ginger (Zingiber officinale) on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. *Cytokine.* 2020;135:155224. doi:10.1016/j.cyto.2020.155224
32. Sheikhhossein F, Borazjani M, Jafari A, et al. Effects of ginger supplementation on biomarkers of oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN.* 2021;45:111-119. doi:10.1016/j.clnesp.2021.07.010
33. Daily JW, Zhang X, Kim DS, et al. Efficacy of ginger for alleviating the symptoms of primary dysmenorrhea: a systematic review and meta-analysis of randomized clinical trials. *Pain Med.* 2015;16(12):2243-55. doi:10.1111/pme.12853
34. Michaelsson G. Decreased concentration of selenium in whole blood and plasma in acne vulgaris. Acta Derm Venereol. 1990;70(1):92.
35. Lim S-K, Ha J-M, Lee Y-H, et al. Comparison of vitamin D levels in patients with and without acne: a case-control study combined with a randomized controlled trial. *PLOS ONE.* 2016;11(8):e0161162. doi:10.1371/journal.pone.0161162
36. Ozuguz P, Dogruk Kacar S, Ekiz O, et al. Evaluation of serum vitamins A and E and zinc levels according to the severity of acne vulgaris. *Cutan Ocul Toxicol.* 2014;33(2):99-102. doi:10.3109/15569527.2013.808656
37. Dreno B, Amblard P, Agache P, et al. Low doses of zinc gluconate for inflammatory acne. *Acta Derm Venereol.* 1989;69(6):541-3.
38. Thomas J. Role of zinc in acne: a study of 77 patients. *International Journal of Research in Dermatology.* 2018;4(3)doi:10.18203/issn.2455-4529. *Int J Res Dermatol.* 20182980
39. Dattola A, Silvestri M, Bennardo L, et al. Role of vitamins in skin health: a systematic review. *Curr Nutr Rep.* 2020;9(3):226-235. doi:10.1007/s13668-020-00322-4
40. Levin J, Momin SB. How much do we really know about our favorite cosmeceutical ingredients? *J Clin Aesthet Dermatol.* 2010;3(2):22-41.
41. Shalita AR, Falcon R, Olansky A, et al. Inflammatory acne management with a novel prescription dietary supplement. *J Drugs Dermatol.* 2012;11(12):1428-33.
42. Razavi M, Jamilian M, Kashan ZF, et al. Selenium supplementation and the effects on reproductive outcomes, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome. *Hormone and Metabolic Research.* 2016;48(03):185-190. doi:10.1055/s-0035-1559604
43. Lee YB, Byun EJ, Kim HS. potential role of the microbiome in acne: a comprehensive review. *J Clin Med.* 2019;8(7)doi:10.3390/jcm8070987
44. Wiertsema SP, van Bergenhenegouwen J, Garssen J, et al. The interplay between the gut microbiome and the immune system in the context of infectious diseases throughout life and the role of nutrition in optimizing treatment strategies. *Nutrients.* 2021;13(3)doi:10.3390/nu13030886
45. Deng Y, Wang H, Zhou J, et al. Patients with Acne Vulgaris Have a Distinct Gut Microbiota in Comparison with Healthy Controls. *Acta Derm Venereol.* 2018;98(8):783-790. doi:10.2340/00015555-2968
46. Noureldein MH, Eid AA. Gut microbiota and mTOR signaling: Insight on a new pathophysiological interaction. *Microb Pathog.* 2018;118:98-104. doi:10.1016/j.micpath.2018.03.021
47. Thompson KG, Rainer BM, Antonescu C, et al. Minocycline and Its Impact on Microbial Dysbiosis in the Skin and Gastrointestinal Tract of Acne Patients. *Ann Dermatol.* 2020;32(1):21-30. doi:10.5021/ad.2020.32.1.21
48. Goodarzi A, Mozafarpoor S, Bodaghabadi M, et al. The potential of probiotics for treating acne vulgaris: A review of literature on acne and microbiota. *Dermatol Ther.* 2020;33(3):e13279. doi:10.1111/dth.13279
49. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol.* 2011;9(4):244-53. doi:10.1038/nrmicro2537
50. Aguwa C, Enwereji N, Santiago S, et al. Targeting dysbiosis in psoriasis, atopic dermatitis, and hidradenitis suppurativa: an updated review of the gut-skin axis and microbiome-directed therapy. *Clin Dermatol.* 2023;doi:10.1016/j.clindermatol.2023.09.019
51. Yan HM, Zhao HJ, Guo DY, et al. Gut microbiota alterations in moderate to severe acne vulgaris patients. *J Dermatol.* 2018;45(10):1166-1171. doi:10.1111/1346-8138.14586
52. Yoshitake R, Nakai H, Ebina M, et al. Beneficial effect of heat-killed lactiplantibacillus plantarum l-137 on skin functions in healthy participants: a randomized, placebo-controlled, double-blind study. *Front Med (Lausanne).* 2022;9:912280. doi:10.3389/fmed.2022.912280
53. Salvi PS, Cowles RA. Butyrate and the intestinal epithelium: modulation of proliferation and inflammation in homeostasis and disease. *Cells.* 2021-07-14 2021;10(7):1775. doi:10.3390/cells10071775
54. Canani RB, Costanzo MD, Leone L, et al. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World J Gastroenterol.* 2011;17(12):1519-28. doi:10.3748/wjg.v17.i12.1519
55. Lolou V, Panayiotidis MI. Functional role of probiotics and prebiotics on skin health and disease. *Fermentation.* 2019-05-17 2019;5(2):41. doi:10.3390/fermentation5020041
56. Santer M, Lawrence M, Renz S, et al. Effectiveness of spironolactone for women with acne vulgaris (SAFA) in England and Wales: pragmatic, multicentre, phase 3, double blind, randomised controlled trial. *BMJ.* 2023;381:e074349. doi:10.1136/bmj-2022-074349
57. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. *J Am Acad Dermatol.* 2000;43(3):498-502. doi:10.1067/mjd.2000.105557
58. Meissner HO, Mscisz A, Reich-Bilinska H, et al. Hormone-balancing effect of pre-gelatinized organic maca (lepidium peruvianum chacon): (iii) clinical responses of early-postmenopausal women to maca in double blind, randomized, Placebo-controlled, crossover configuration, outpatient study. *Int J Biomed Sci.* 2006;2(4):375-94.
59. Gonzales GF, Gasco M, Lozada-Requena I. Role of maca (Lepidium meyenii) consumption on serum interleukin-6 levels and health status in populations living in the Peruvian Central Andes over 4000 m of altitude. *Plant Foods Hum Nutr.* 2013;68(4):347-51. doi:10.1007/s11130-013-0378-5
60. Dording CM, Fisher L, Papakostas G, et al. A double-blind, randomized, pilot dose-finding study of maca root (L. meyenii) for the management of SSRI-induced sexual dysfunction. *CNS Neurosci Ther.* 2008;14(3):182-91. doi:10.1111/j.1755-5949.2008.00052.x
61. Michaelsson G, Berne B, Carlmark B, et al. Selenium in whole blood and plasma is decreased in patients with moderate and severe psoriasis. *Acta Derm Venereol.* 1989;69(1):29-34.
62. Grether-Beck S, Marini A, Jaenicke T, et al. Molecular evidence that oral supplementation with lycopene or lutein protects human skin against ultraviolet radiation: results from a double-blinded, placebo-controlled, crossover study. *Br J Dermatol.* 2017;176(5):1231-1240. doi:10.1111/bjd.15080
63. Weinbrenner T, Fito M, de la Torre R, et al. Olive oils high in phenolic compounds modulate oxidative/antioxidative status in men. *J Nutr.* 2004;134(9):2314-21. doi:10.1093/jn/134.9.2314
64. Nobile V, Burioli A, Yu S, et al. Photoprotective and antiaging effects of a standardized red orange (citrus sinensis (l.) osbeck) extract in Asian and Caucasian subjects: a randomized, double-blind, controlled study. *Nutrients.* 2022;14(11) doi:10.3390/nu14112241
65. Amer RI, Ezzat SM, Aborehab NM, et al. Downregulation of MMP1 expression mediates the anti-aging activity of Citrus sinensis peel extract nanoformulation in UV induced photoaging in mice. *Biomed Pharmacother.* 2021;138:111537. doi:10.1016/j.biopha.2021.111537
66. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem Pharmacol.* 2008;75(4):787-809. doi:10.1016/j.bcp.2007.08.016
67. Gamret AC, Price A, Fertig RM, et al. Complementary and alternative medicine therapies for psoriasis: a systematic review. *JAMA Dermatol.* 2018;154(11):1330-1337. doi:10.1001/jamadermatol.2018.2972
68. Sandoval AGW, Vaughn LT, Huang JT, et al. Role of tumor necrosis factor-alpha inhibitors in the treatment and occurrence of acne: a systematic review. *JAMA Dermatol.* 2023;159(5):504-509. doi:10.1001/jamadermatol.2023.0269
69. Panahi Y, Fazlolahzadeh O, Atkin SL, et al. Evidence of curcumin and curcumin analogue effects in skin diseases: A narrative review. *J Cell Physiol.* 2019;234(2):1165-1178. doi:10.1002/jcp.27096
70. Antony B, Merina B, Iyer VS, Judy N, Lennertz K, Joyal S. A pilot cross-over study to evaluate human oral bioavailability of BCM-95CG (Biocurcumax), a novel bioenhanced preparation of curcumin. *Indian J Pharm Sci.* 2008;70(4):445-9. doi:10.4103/0250-474X.44591
71. Del Rosso J, Farris PK, Harper J, et al. New insights into systemic drivers of inflammation and their contributions to the pathophysiology of acne. *J Drugs Dermatol.* 2024;23(2):90-96. doi:10.36849/JDD.8137

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