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A review on oral supplements and herbal remedies in the treatment of *Acne vulgaris*

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Abstract
Acne vulgaris (AV) is one of the most common skin disorders in the world, costing the US alone 3 billion dollars in treatment costs and productivity losses. AV is an inflammatory disorder involving the pilosebaceous unit resulting from the interplay of genetics, hormonal influences, immune function, and environmental factors. The complex pathogenesis involves dysbiosis of the hair follicle and sebaceous gland microbiome, bacterial colonisation by *Cutibacterium acnes*, androgen-dependent stimulation, and innate and acquired immune responses. This leads to non-inflammatory lesions, such as open and closed comedones, and inflammatory lesions, such as pustules, nodules, and cysts. Although AV is not physically disabling, the psychological impact drives many people to seek treatment. Typical medical treatment for those suffering from AV include topical therapies, systemic antibiotics, hormonal agents, and retinoids. Because of side effects associated with these medications, patients will seek out "natural" treatments. There are numerous misconceptions about the benefits of oral supplements and herbal remedies. In this review, we discuss probiotics, antioxidants, omega 3 fatty acids, nicotinamide, and herbal remedies founded in Traditional Chinese Medicine (TCM) and their effectiveness. We found that there is some evidence for nicotinamide, antioxidants, and probiotics as adjuvant therapies, but no evidence for use as monotherapy. Omega 3 fatty acid supplementation seems to be beneficial. Finally, the evidence for herbal remedies in the treatment of AV is too limited and the quality too poor to recommend them. Based on these results, dermatologists should keep complimentary oral supplements in their repertoire for patient care.

Keywords: *Acne vulgaris*, herbal, oral, supplements, treatment

Introduction
Acne vulgaris (AV) is a chronic inflammatory skin condition affecting, in some regions, up to 90% of adolescents [1]. It typically begins in the pre-adolescent period (ages 7 to 12 years), as acne is hormone-sensitive. Though the ubiquity of AV decreases with increasing age, up to 35% of women report experiencing acne in their third decade of life [2]. Seborrhea, comedones, and erythematous papules and pustules are the most common clinical presentations of acne, though rarer forms may also be found [3]. Although acne is not associated with any change in mortality, it leads to significant morbidity through psychological distress related to perceived appearance, scarring, negative self-image, and depressive thoughts [4]. The mainstays of AV treatment include topical and systemic medicines; after six to eight weeks the treatment efficacy is weighed against side effects and sometimes a new treatment plan is put into place. Treatment regimens for AV include benzoil peroxide, retinoids, isotretinoins, azelaic acid, salicilic acid, keratolytic soaps, alpha hydroxy acids, and other hormonal and anti-seborrheic medications [5]. However, because of acne's ubiquity and psychological impact, numerous other therapies have been utilized in the treatment of AV. Chemical peels, intralesional steroid injections, microdermabrasion, radiofrequencies, light therapies, and lasers are commonly utilized, though none are free of side effects and all have questionable efficacy [6]. Due to the oftentimes severe side effects seen with many AV medications, patients often seek "natural" medicines as they are perceived to be safer [7]. However, many alternative approaches to AV treatment are tried without evidence of efficacy or safety. We have reviewed the published literature for the use of common oral supplements, herbal remedies, and other oral complementary medicines in the treatment of AV. Current evidence suggests that antioxidants, probiotics, and omega 3 fatty acids can be an effective complementary tool for dermatologists but should not be utilized on their own. Oral nicotinamide has been shown to be effective when combined with other oral supplements, such as antioxidants, but there is no evidence to show that oral nicotinamide is efficacious as a monotherapy. Finally, current evidence is insufficient to recommend Chinese herbal medicines as a treatment for AV. Further study is warranted on oral supplementation in AV to determine possible benefits of these over-the-counter remedies.

Fig 1: Comedones (open and closed) with post-inflammatory hyperpigmentation in an adult female [26].
Photo courtesy of Bethanee Schlosser, MD, PhD.

Fig 2: Inflammatory papules and pustules in an adult female [26].
Photo courtesy of Bethanee Schlosser, MD, PhD.

Antioxidants

Antioxidants are substances that protect your cells against free radicals produced in your body. Zinc and vitamin A are commonly utilized oral antioxidants because of their relatively few side effects [8]. Antioxidants were first postulated to have a role in the treatment of AV because those experiencing acne are under an increased inflammatory state causing systemic oxidative stress [9]. This leads to an increase in waste substances produced by cells and an inability for the body to process and remove free radicals efficiently, which will harm your cells and can cause flaring of AV. During the normal process of bodily detoxifying, glucose-6-phosphate dehydrogenases and glutathione peroxidases can efficiently remove reactive oxygen species. However, both are decreased in patients with AV [10].

Zinc has been well documented as being an efficacious treatment of AV. After 12 weeks of treatment with zinc supplementation, the average decrease in acne, a subjective score grading the severity of disease based on the dominant lesions, evaluating inflammation present, and estimating the extent of skin involvement, was approximately 70% in both male and females. However, the extensive bioavailability of some zinc supplements, such as zinc gluconate, has been shown to play a role in how effectively it increases AV remission [10]. Various studies have shown that zinc levels are lower in patients with AV, and therefore treatment with an oral zinc supplement can be therapeutic [11]. Vitamin A has also been found in lower levels in AV patients as compared to their age-matched controls, it is generally not considered a useful oral supplementation [12]. However, it is an extremely useful medication in higher doses than would be considered “supplementation." Epigallocatechin-3-gallate polyphenol, a compound found in green tea, has been proposed as a treatment for AV due to its anti-inflammatory and anti-oxidant activity. However, most studies have only looked at topical treatments of this drug and the evidence for oral supplementation is limited [13]. Finally, low blood levels of selenium have been documented in acne patients. One study found that by a combination of selenium and vitamin E tablet taken once daily led to improvements in perceived acne [14].

At this time, the recommendations are that antioxidants can be an important tool for dermatologists. However, they are not a replacement for medications and should be used as complementary therapies. There is evidence that oral supplementation can be effective, but further studies are required to fully understand their role in AV.

Nicotinamide

Nicotinamide is a hydrophilic form of vitamin B3 or niacin. It is endogenously created when you consume niacin-rich foods such as fish or eggs. The benefit of nicotinamide over niacin is that nicotinamide does not cause the same gastrointestinal or vasodilatory systemic effects [15]. Though nicotinamide is often used as a topical therapy, we will be discussing the variety of roles the oral supplement plays in the treatment of AV. To begin, nicotinamide provides a substrate for PARP-1, a nuclear enzyme that is important for the body to fight against AV. As well, it decreases the *in vitro* secretion of interleukin-8, a cytokine that is secreted in response to a number of pathogens, with *P. Acnes* being one of them. Therefore, it also exerts an anti-inflammatory effect via cytokines [16]. Niren & Torok (2006) demonstrated that nicotinamide, when taken in combination with zinc, copper, and folic acid, caused a tremendous improvement in patients with moderate AV. In all studies looking at oral nicotinamide as a therapy, no side effects were reported[17].Finally, patients who had taken NicAzel, an oral supplement that combined nicotinamide, azelaic acid, zinc, pyridoxine, copper, and folic acid were studied [18]. By week 8, around 76% of patients reported that their skin was cleared just as effectively as 8 weeks on oral antibiotics. However, this study never looked at oral nicotinamide alone, and the scoring system was highly subjective.

Based on the current literature, oral nicotinamide can be recommended as an efficacious therapy when combined with other oral supplements. However, there is no evidence that oral nicotinamide is effective on its own.

Omega 3 fatty acids

Omega 3 fatty acids can be categorized into three main groups: Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). They are mainly found in fish, nuts, and seeds. Omega-3s make up an important component of your cellular membranes, and therefore need to be synthesized or supplemented. Omega-3s were first postulated to have a role in AV therapy when it was noted that societies that consume high fat diets, such as France, have low levels of AV compared to the United States where sugars are more prevalent [19].

A study conducted by Rubin *et al*. in Beverly Hills examined the effect of a supplement containing EPA and antioxidants on five patients with mild-to-moderate acne for 2 months demonstrated a decrease in inflammatory acne lesion count.

Inflammatory acne lesion count was significantly reduced in all patients [20]. This study also found that consumption of an omega-3 fish oil-based nutrient combination appeared to have some positive effect on lesions and the mental outlook of the subjects. 4 of 5 individuals experienced reduced lesion count, with none experiencing worsening. However, there were only 5 cases cited in this study. Additionally, chromium, zinc, and selenium were also consumed along with omega-3. Another study done by Jung *et al*. found that mean inflammatory and non-inflammatory acne lesion counts were significantly reduced at end of the study in omega-3 and y-linoleic groups not in the control group. Severity also decreased of the period for both groups, while control remained the same. The subjective assessment of the patients followed the same pattern. Finally, its been found that the ratio of omega-3:omega-6 plays a role in inflammation and omega-3 seems to play a role in glycemic regulation by decreasing IGF-1. As inflammation and high-glycemic indexes seem to promote acne, higher levels of omega-3 could theoretically play a role in reducing acne severity [21]. This was a literature review, indicating that more research needs to be done on omega-3 and acne and their relationship.

Taken all together, omega-3 seems to have a role in the reduction of acne vulgaris. However, there needs to be more specific and focused research done before any strong recommendations can be made.

Probiotics

Probiotics are live bacteria and yeast that are classified mainly into three groups: Lactobacilli, bifidobacterium, and enterococci [22]. They are meant to offer health benefits to the patient when given in the appropriate dose, which is a larger amount than most people think. This is especially important when you consider the gut-brain-skin axis [23]. Acne vulgaris pathogenesis involves increased and altered sebum production under androgen control, follicular keratinization, and follicular colonization by *Cutibacterium acnes*, all of which are increased by a stressful state [24].

Probiotics have been hypothesized to be beneficial in the treatment of AV for numerous reasons. To begin, probiotics have been proven to decrease levels of *C acnes* in the skin flora, as well as decrease sebum production. They also decrease inflammation due to the downregulation of inflammatory cytokines and the recruitment of cytotoxic T cells [25]. Antibiotics are commonly utilized in the treatment of AV; however, as systemic antibiotics kill off beneficial intestinal microorganisms, probiotics can be utilized to replenish the "good" gut bacteria [26]. A study by Kim *et al*. showed that probiotic supplementation via fermented dairy milk improved acne in all clinical dimensions specified within 12 weeks. Jung *et al*. showed that the total number of lesions significantly improved in females taking minocycline and probiotics versus minocycline alone. Finally, Robert H Silver in 1961 found that a variety of Lactobacillus strains in supplements improved acne in 80% of test subjects. Similarly, a study out of Russia evaluated acne patients for impaired bacterial microflora, and patients received intestinal “micro-flora correcting agents” in addition to traditional acne therapy. A more rapid clinical improvement was noted in those receiving the supplement [27].

Unfortunately, most studies that look at probiotic supplementation encounter problems regarding the heterogeneity of the strain, dosing, and timing of therapy.

Based on the current literature, there is evidence to suggest that oral probiotics can be effective as an adjunct therapy to managing AV. Larger studies looking at probiotic supplementation in conjunction with medications are needed to understand the true advantages and disadvantages of probiotics.

Oral supplements in AV

Table 1: A summary of synbiotics and outcomes in meta-analysis by Goordarzi *et al*.

Study	Synbiotic strain	Outcome
Bowe *et al*. 2006[4]	*Streptococcus salivarius, Enterococcus faecalis*	Of the 106 participants recruited, with mean age 28.4 (SD 8.1), 33.3% showed inhibition of *P. acnes* and 39.4% inhibited GAS growth
Wang *et al*. 2014 [29]	*Streptococcus epidermidis, Paenibacillussp.*	The number of *P. acnes* colonies that grew without the combination of skin microorganisms was over three logs higher than the number of *P. acnes* colonies that grew with the skin microorganisms ($P < 0.001$)
Cosseau *et al*. 2008[7]	*Lactobacillus paracasei*	Significant reduction ($P < 0.05$) Grade III and IV acne, which is often the cause of more severe inflammatory acne
Oh *et al*. 2006 [21]	*Lactobacillus sp.*	The bacteriocin produced by *Lactococcus* sp. inhibited the growth of *S. epidermidis, S. aureus, Strep. pyogenes*, and *P. acnes*. The bacteriocin also caused a rapid inactivation of *P. acnes*, with no allergic reactions or irritations seen
Gueniche *et al*. 2010 [19]	*Lactobacillus paracasei*	*Lactobacillus paracasei*decreased vasodilation, edema, mast cell degranulation and TNF-alpha release artificially induced by *P. acnes* as compared to control

AV, Acne vulgaris; GAS, Group A Streptococcus

Chinese herbal medications

Traditional Chinese Medicine (TCM) is a branch of medicine that is based on over 3,500 years of Chinese medicinal practices such as massage, acupuncture, herbal remedies, and much more. TCM is one of the most pervasive non-Western-medicine practices in North America and is utilized frequently in the treatment of diseases such as diabetes and atopic dermatitis. Because acne develops as a general result of sebum overproduction and inflammation, and many Chinese traditional medicines have anti-inflammatory properties, it is logical to suggest that Chinese herbal medications could be beneficial for the treatment of acne vulgaris [28].

Some low-quality evidence from single trials suggest that tea tree oil & purified bee venom may reduce the total lesion count in acne vulgaris. However, some mildly adverse effects were found as well, and were also encountered during other herbal treatments, acupuncture, and wet cupping. This paper has a limited sample size and self-reporting also has limitations [29]. Herbal mask therapy was found to be more effective when combined with bloodletting and cupping [30]. This combination was more effective than the control group and had higher success rates, but there were only 37 participants in this study, and there were numerous

confounding factors like bloodletting and cupping. Plant extracts and phytochemicals are promising treatments for mild to moderate acne [31]. No severe adverse effects were reported, and most studies examined showed some positive effects. The authors call out for more rigorous research on the topic and for standardized methods of grading acne and assessing therapeutic effects. These were generally low-quality studies (12 of 23) with lacking information as to whether they were blinded or not. Compound Oldenlandis Mixture (COM) (unknown mixtures of Chinese herbs) was compared against the control group (given Chinese angelica and flavescent sophora) in an RCT with 120 participants [31]. It was found that COM was significantly more effective for treating acne - measuring the percentage change in lesion count. Limitations in this study were: baseline severity was not described, actual lesion count data was not given, and it was unclear as to the appropriateness of the control.

Based on the research, there is no evidence to suggest that dermatologists should recommend Chinese herbal medications to their patients for the treatment of the acne vulgaris.

Methods

A literature search was performed using the databases Cochrane, Medline, PubMed, SciFinder, SCOPUS, Wiley Online, and AMED (Allied and Complementary Medicine).

Table 2: Criteria utilized for literature search.

Search terms:	*Acne vulgaris*, complementary, oral, supplements, herbal, non-traditional, and treatment
Inclusion criteria:	Only oral supplements and complimentary medicines were included as treatment modalities. Studies must directly involve subjects with at least mild acne and must use a human model.
Exclusion criteria:	Topical or procedural treatments

Conclusion

Acne vulgaris is a common and unpleasant condition in which the treatments often yield further unpleasant side effects. Many studies about oral supplements in the treatment of AV using complementary therapies often have poor methodology or small sample sizes. However, recent data has shown that some oral supplements, such as probiotics, antioxidants, nicotinamide, and omega-3 fatty acids may prove to be efficacious. Additionally, these oral supplements tend to be inexpensive and relatively harm-free and therefore dermatologists could suggest them to patients after discussing the risks and benefits. However, more research needs to be done before the true efficacy of oral supplements in acne vulgaris is discovered.

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