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A Biologically Based Approach to Acne and Rosacea

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ABSTRACT

Complementary and alternative medicine (CAM) therapies are increasing in popularity in the field of dermatology. Natural products and holistic approaches are in high demand among patients and research has begun to support their roles in acne and rosacea pathophysiology. In this article, commonly utilized biologically based complementary and alternative therapies for acne and rosacea are reviewed from an evidence-based perspective. Therapies discussed include vitamin C, nicotinamide, zinc, tea tree oil, green tea, resveratrol, curcumin, feverfew, licorice, chamomile, polypodium leucotomos, and nutrition-based approaches. J Drugs Dermatol. 2018;17(6):611-617.

INTRODUCTION

Alternative medicine is a term used for treatments that are used in place of evidence-based, standard Western medical care. Complementary medicine, which combines these less-mainstream approaches with conventional medicine is used more often.[1,2] In the United States, it is estimated that more than 30% of adults and 12% of children use health care practices outside of traditional Western medicine,[2] translating to $34 billion spent annually on complementary and alternative medicine (CAM).[3] The most common complementary health approach used by Americans in the 2012 National Health Interview Survey was natural products (17.7%), which includes herbs (also known as botanicals), vitamins, minerals, dietary supplements, and probiotics.[2] Along with foods and special diets, natural products make up biologically based practices of CAM.[1]Patients are often frustrated by the chronicity of dermatologic conditions, and this may compel them to experiment with CAM therapies.[4] Results from the 2007 National Health survey revealed that among those reporting skin problems in the United States, 84.5% used CAM that year,[5] an increase from 49.2% in 2002.6 In a recent study, patients using CAM treatments for acne thought that CAM therapies had less potential for adverse effects and were more efficacious than mainstream topical therapies.[7] With increased patient interest in CAM and heightened insight into their role on cutaneous disease processes, it is imperative that dermatologists be made aware of these advances to make appropriate recommendations to patients. The goal of this article is to detail the best evidence for commonly utilized biologically based CAM practices employed for two common dermatoses with significant societal impacts: acne and rosacea.

Acne

Antioxidants 1. Vitamin CVitamin C (ascorbic acid) is both an antioxidant and anti-inflammatory agent commonly used topically for skin protection in various dermatologic conditions.[4,8] Due to its chemical instability, vitamin C is available in numerous modified formulations that improve stability, with sodium ascorbyl phosphate (SAP) being commonly studied and commercially available.9 SAP may have utility in the

treatment of acne due to its strong antimicrobial activity on P. acnes and through reduction of lipid oxidation, which may then lead to a decrease in inflammation and follicular keratinization.8 Several studies have reported the efficacy of topical SAP for the treatment of acne both alone and in combination with other medications. Klock et al reported that 5% SAP cream was more efficacious than 5% benzoyl peroxide (BP) cream for the treatment of acne vulgaris in a 12-week open-label study of 60 patients.[8] A randomized control trial (RCT) by Ruamrak et al. found that 5% SAP and 0.2% retinol had synergistic effects in the reduction of inflammatory acne lesions.[10] Another RCT demonstrated that monotherapy with 5% SAP lotion led to improvements in Investigator's Global Assessment Scores, Subject's Global Assessment Scores, and lesion counts when compared to vehicle.[11]2. NicotinamideNicotinamide, also known as niacinamide, is a form of vitamin B3 regarded as a potential therapy for acne due to its potent anti-inflammatory and antioxidant effects.[12] Nicotinamide may reduce comedogenesis via various mechanisms. Draelos et al. performed two separate clinical trials in Japan and the USA to evaluate the effect of 2% topical nicotinamide on sebum production and sebum levels. In the Japanese group, sebum

excretion rate was significantly reduced after 2 and 4 weeks of use, while in the Caucasian group sebum levels were reduced, but sebum excretion rate was not significantly reduced after 6 weeks of use.[13] Nicotinamide also inhibits P. acnes production of interleukin-8 (IL-8) through the NF-kappaB and MAPK pathways in keratinocytes.[14] In a 1995 randomized, double-blind, placebo-controlled trial, 4% nicotinamide gel appeared to be more efficacious than 1% clindamycin gel for moderate inflammatory acne, though this was not statistically significant. In a multi-center randomized trial, 4% nicotinamide emulsion was more effective than both 1% clindamycin emulsion and the vehicle control.[15] Interestingly, combination topical nicotinamide-clindamycin products showed no difference when compared to clindamycin-only products in two studies.[16,17] These data indicate that topical nicotinamide may be an attractive alternative to topical clindamycin, as it does not carry a risk of antibiotic resistance and has a similar side effect profile consisting largely of application site reactions.[18,19] While a few studies have shown some benefit of oral nicotinamide in acne vulgaris, they are confounded by the use of other supplements used in combination.[20,21]3. ZincZinc is an essential trace element that decreases oxidative stress and has demonstrated bacteriostatic effect against P. acnes.[22,23] Zinc is utilized to improve the efficacy of topical antibiotics in combination preparations. In multiple studies, the addition of 1.2% zinc acetate to 4% topical erythromycin was shown to form a complex that enhances the penetration of erythromycin into the skin.[22,24,25] Daily oral zinc gluconate supplementation (30 mg) for 2 months reduced the number of inflammatory acne lesions in a small study of 30 patients.[26] An oral methionine-based zinc antioxidant complex containing vitamin C, mixed carotenoids, d-alpha-tocopherol acetate and chromium showed a significant improvement in acne when taken three times daily for 3 months.[27] In a multi-center, prospective study of 235 patients with inflammatory acne, the addition of a novel prescription dietary supplement containing zinc oxide, nicotinamide, azelaic acid, pyridoxine, copper and folic acid (NicAzel, Elorac Inc, Vernon Hills, IL) resulted in a statistically significant improvement of acne severity after 4 and 8 weeks of use.[21] Additionally, oral zinc gluconate appears to be a safe option in the management of acne in pregnant patients. A retrospective review on zinc gluconate supplementation in doses less than 75 mg daily found no harmful fetal effects.[28] *Botanicals* 1. Tea tree oilTea tree, or malaleuca oil (TTO) is an essential oil derived from the leaves of the Australian native plant Malaleuca alternifolia. TTO is an ingredient included in many over the counter products targeting acne, including face and body washes, toners, masks, gels and lotions.[29] In fact, TTO is the second most commonly used topical acne product, with 2.5% benzoyl peroxide being the most commonly used product.[30] TTO has evidence of broad-spectrum antimicrobial activity as well as anti-inflammatory properties which may be useful in the treatment of acne.[31] In a study of 124 patients comparing 5% TTO gel to 5% benzoyl peroxide, both significantly reduced the number of both inflamed and non-inflamed acne lesions. The TTO treated group had fewer side effects, however the onset of action was slower than the 5% benzoyl peroxide goup.[32] Enshaieh et al. performed a randomized, double-blind, placebo-controlled clinical trial in 60 patients to determine the efficacy of 5% TTO for acne vulgaris and found a significant improvement in total lesion counts and acne severity index compared to placebo.[33] A number of cases, however, have reported allergic contact dermatitis as a result of TTO use, with positive patch test reactions ranging from 0.1% to 3.5%.[34]2. Green teaGreen tea is produced from fresh leaves of the plant, Camellia sinensis, using a method that prevents oxidation of polyphenolic compounds called catechins.[35] The most abundant, extensively studied and therapeutically beneficial catechin found in green tea is (-)-epigallocatechin-3-gallate (EGCG).[36] Besides its antimicrobial activity, in vitro studies suggest that EGCG exerts its effect in acne by suppressing sebum production though inhibition of 5-alpha reductase while reducing inflammation and inducing apoptosis of human sebocytes.[37-39] In fact, a 3% green tea emulsion significantly reduced sebum production in a recent study in healthy human volunteers.[40] EGCG and green tea polyphenols also work by combatting reactive oxygen species and preventing lipid peroxidation, protecting glutathione peroxidase and subsequently restoring glutathione levels.[41] In an open-label study of 20 patients with mild-to-moderate acne vulgaris, twice-daily application of

2% green tea lotion decreased mean total lesion count by approximately 58% after 6 weeks.[42]3. ResveratrolResveratrol (3,4,5-trihydroxy-transtilbene) is a phytoalexin found in spermatophytes such as grapes, peanuts, mulberries, spruce and eucalyptus.[4] Resveratrol has demonstrated antimicrobial effects against P. acnes in vitro as well as potent antioxidant and anti-inflammatory properties.[43] Resveratrol may also play a role in the inhibition of sebocyte growth via inactivation of the Akt pathway.[44] A single-blind study of 20 patients with acne vulgaris revealed a reduction in the Global Acne Grading System scores, a mean reduction in the average areas of microcomedones, and a significant decrease in lesions in areas treated with a resveratrol-containing hydrogel compared to vehicle control.[45]5. CurcuminCurcumin, a phytochemical derived from the spice turmeric, has demonstrated antimicrobial activity against P. acnes,[46,47] as

well as anti-oxidant and anti-inflammatory effects.[48] In a randomized, double-blind study of 53 patients, the combination of oral curcumin and a topical curcumin cream was more effective at 4 weeks compared to placebo, oral curcumin alone and oral curcumin combined with a topical curcumin gel.[49] *Diet*The association between diet and acne is a controversial. Some of the most compelling evidence lies in the link between acne and dietary glycemic load, a direct measure of insulin and blood glucose increasing potential.[50] Ingestion of a high-glycemic load triggers a cascade of endocrine responses that promote acne formation via androgens and growth hormones.[4,50] In a RCT of 43 men, adherence to a low-glycemic-load (LGL) diet resulted in a significant decrease in acne lesion counts and insulin sensitivity compared to controls.[51,52] Another RCT of 32 patients demonstrated significant clinical improvement of inflammatory and non-inflammatory acne lesions in the LGL diet group with corresponding decreases in inflammation and sebaceous gland size on histopathology.[53] Multiple reports by Adebamowo indicate a relationship between dairy products, particularly skim milk, and acne exacerbations, which may be due to hormonal constituents and increases in plasma IGF-1.[54,55] The gut-brain-skin hypothesis proposed by Stokes and Pillsbury suggests a relationship between emotional stress, alterations in the microbial flora within the gastrointestinal tract, local and systemic inflammation, and the therapeutic utility of probiotics.[56] However, clinical studies supporting the role of probiotics as adjuvant acne therapy are limited. A Russian study reported faster clinical improvement when oral probiotics were combined with standard acne therapy.[57] Similarly, a prospective, open-label study of 45 women showed a significant decrease in total acne lesion counts at 8 and 12 weeks in patients receiving both oral probiotics and minocycline compared to those receiving probiotics or minocycline alone.[58] One study found that a topical probiotic lotion resulted in a 60% reduction in inflammatory lesions and 20% reduction in comedones at 8 weeks compared to placebo.[59]

Rosacea

*Nicotinamide*Nicotinamide, or niacinamide, may be beneficial in the treatment of rosacea due to its ability to mitigate the inflammatory response and stabilize epidermal barrier function.[60] In a pilot study of 34 patients with rosacea treated with a gel containing a metabolite of nicotinamide known as 1-methylnicotinamide, 26 patients (76.5%) achieved clinical improvement.[61] A study of two moisturizers containing nicotinamide and glycerin revealed improved skin hydration as measured by corneometry and improved barrier integrity as measured by transepidermal water loss.[62] Draelos et al conducted a randomized, investigator-blind study in 50 subjects with rosacea comparing a nicotinamide-containing moisturizer applied twice daily for 4 weeks to the face and one forearm to an untreated control. In this study, the nicotinamide-containing moisturizer improved stratum corneum barrier function and hydration of the face.[63] In an open-label, multicenter, prospective study of 198 patients with acne and/or rosacea, an oral formulation consisting of 750 mg nicotinamide, 25 mg zinc, 1.5 mg copper, and 500 µg folic acid that was given twice daily for 4 and 8 weeks showed equivalent clinical response and patient satisfaction when compared with patients taking concomitant oral antibiotic therapy. In addition, approximately 55% reported moderate or substantial improvement in inflammatory lesions, which was statistically significant.[20] There is a slight discrepancy between the formulation studied and the commercially available product, which consists of 750 mg nicotinamide, 27 mg zinc, 2 mg copper, 500 µg folic acid, 50 µg selenium and 100 µg chromium.[20,64] Whether these slight differences would result in a clinically significant change in response than that reported in this study is not known.*Botanicals*1. Feverfew Feverfew (Tanacetum parthenium, Chrysanthemum parthenium) is a perennial herb from the daisy family with a long history of medicinal use in treating fever, migraines, and arthritis.[4,65] One of its active components, parthenolide, limited feverfew's use as a topical agent due to reports of skin sensitization. More recently, however, a parthenolide-free extract of feverfew (PFE) has been developed that maintains feverfew's anti-inflammatory properties without the risk of creating a contact allergy.[4] PFE inhibits the activity of pro-inflammatory enzymes 5-lipoxygenase, phosphodiesterase-3, and phoosphodiesterase-4, reducing the release of pro-inflammatory mediators such as nitric oxide, prostaglandin-E2, TNF-alpha, IFN-gamma, and interleukins 2 and 4.[66] In a study by Martin et al, PFE had greater free radical scavenging

activity against a wide range of reactive oxygen species compared to vitamin C. Additionally, PFE reduced UV-induced hydrogen peroxide formation and pro-inflammatory cytokine release and also decreased epidermal hyperplasia, DNA damage and apoptosis in vitro. The same group also conducted a randomized, placebo-controlled, double-blinded study of 12 subjects with Fitzpatrick skin types II and III and found that topically applied PFE significantly reduced erythema 24 hours post-UV exposure compared to controls.[67]2. LicoriceThe genus Glycyrrhiza is composed of 30 species of licorice plants utilized in Chinese medicine for the treatment of a myriad of diseases.[68] Glabridin is a main ingredient with potential photoprotective benefits, showing inhibitory effects on melanogenesis and inflammation when topically applied in UVB-irradiated murine models.[69] In 62 patients with mild-to-moderate erythematotelangiectatic rosacea or red facial skin not attributable to rosacea, a four-product skincare

regimen (Eucerin Redness Relief) containing licochalcone A (Lic A), an anti-irritant from the licorice plant Glycyrrhiza inflata, was instituted for 8 weeks. At both 4 and 8 weeks, there were significant improvements in average erythema scores as well as improved quality of life measured by patient questionnaires. In a subsequent study, patients treated with topical metronidazole who then used the Lic A-containing products for 2 weeks had continued improvement in erythema with no adverse effects.[70] In a prospective randomized vehicle-controlled trial, topical Lic A significantly reduced UV- and shaving-induced erythema compared to controls, further suggesting therapeutic potential for sensitive or irritated skin.[71] 3. Chamomile Chamomile, Matricaria recutita and Chamaemelum nobile, has traditionally been used for its soothing effects on both the gastrointestinal system and cutaneous inflammatory disorders including atopic dermatitis.[68,72] Chamomile flavonoids and terpinoids can inhibit cyclooxygenase, lipoxygenase, and histamine release, exhibiting antioxidant, anti-inflammatory, and antipruritic effects.[4,72,73] In a randomized, placebo-controlled trial, 246 patients with moderate rosacea applied either a golden chamomile (Chrysanthellum indicum) extract-based cream or placebo to the face twice daily for 12 weeks. Subjects in the treatment group experienced significant reduction in erythema scores and overall rosacea severity compared to baseline and placebo with mild adverse reactions that were similar to placebo.[74] 4. Green tea There is some evidence to suggest that the anti-inflammatory and anti-angiogenic properties of EGCG present in green tea may play a role in the prevention of telangiectasias in rosacea. In a small randomized, double blind trial, 4 volunteers with significant erythema and telangiectasias applied a cream containing EGCG to one side of the face and a vehicle control to the other side twice daily for 6 weeks. Biopsies taken from the EGCG treated sites showed significantly decreased expression of the angiogenic factors hypoxia inducible factor-1-alpha and vascular endothelial growth compared to the control sites.[75] EGCG also protects skin against ultraviolet radiation, a known trigger for rosacea. In a study of healthy volunteers exposed to solar simulated radiation who were pre-treated with topical green tea extract or one of its constituents, the EGCG fraction was particularly efficient at inhibiting erythema. Additionally, skin treated with green tea extracts had protected epidermal Langerhans cells and reduced DNA damage after UV radiation.[76] *Photoprotectants* The highly sensitive and easily irritated skin in patients with rosacea often precludes use of commercial sunscreens, causing patients to seek natural alternatives for protection against photo-induced rosacea flares.[4] Vitamin C is a potent antioxidant and anti-inflammatory agent that both promotes collagen synthesis and prevents its degradation when applied topically in its stabilized form.[77] Vitamin E, alpha tocopherol, is a lipid-soluble vitamin that becomes oxidized while protecting hydrophobic cell membranes from free radical lipid peroxidation.[78] In a study using a porcine model, 15% L-ascorbic acid and 1% alpha tocopherol applied in combination provided significant protection against UV-induced erythema and sunburn cell formation. Though equivalent concentrations of both the L-ascorbic acid and alpha tocopherol alone were protective, the combination of the two was superior, yielding 4-fold protection.[79] The same investigators found that adding 0.5% ferulic acid both improved stability and doubled the photoprotection from 4- to 8-fold.[80] Polypodium leucotomos (PL) is a fern plant native to Central and South America that has had success as an oral photoprotectant.[81] In a study of 10 healthy patients with skin phototypes II to III, psoralen-UVA-induced phototoxicity was lower in those using 7.5 mg/kg of oral PL.[82] Another study of subjects with Fitzpatrick skin type I to III exposed to UVB radiation showed a decrease in clinical and colorimetric changes in 17 of the 22 subjects post-PL administration with reduced UV damage biomarkers on histopathology in all subjects.[83] Though theoretical evidence supporting the use of the aforementioned photoprotectants in rosacea is sound, rigorous studies in patients with confirmed rosacea are lacking. *Diet* Diet-related triggers of rosacea have long been acknowledged. Many foods and drinks exacerbate facial erythema in rosacea, including alcohol, spicy foods, coffee, hot drinks, and niacin-containing foods to name a few.[84-87] Recently, attention has shifted to determining which diet-based factors can alleviate rosacea symptoms. Omega-3 fatty acids are utilized in meibomian glands on eyelids for meibum production, and increased dietary intake of omega-3 fatty acids has been shown to alter the composition and clearance of meibum secretions, potentially reducing dry eye symptoms in patients with ocular rosacea.[88-90] Flaxseed oil is a rich, natural dietary source of omega-3 essential fatty acids, comprised of 57% alpha-linolenic acid.[90,91] In a retrospective case series of 27 children

with blepharokeratoconjunctivitis, 3 of which had confirmed acne rosacea, oral flaxseed oil helped stabilize lid margin disease in all 12 patients who used it used as an alternative to long-term antibiotics.[91] In a multi-center randomized control trial of 130 patients with ocular rosacea, significant improvement in dry eye symptoms was achieved following a 6-month course of an omega-3 fatty acid supplement compared to the placebo group.[92] A connection between rosacea and small intestinal bacterial overgrowth (SIBO) was demonstrated in a case control study,

with rosacea patients experiencing significantly higher levels of SIBO compared to controls. Moreover, eradication of SIBO with rifaximin led to a statistically significant improvement in cutaneous lesions including flushing, erythrosis, papules and pustules.[93] Though the mechanism for the development of rosacea is unknown, it is speculated that increased intestinal permeability in SIBO may play a role, with resultant translocation of gut bacteria and pro-inflammatory cytokines into the bloodstream.[94,95] A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP), considered prebiotic substrates, has been used to alter the gut microbiota.[96]

CONCLUSION

There is a large and undeniable consumer demand for CAM in dermatology. Although there is mounting evidence to support the use of some therapies, a significant need to rigorously study these agents remains. Many healthcare providers may still prefer to use traditional medications and procedures as mainstay therapies for acne and rosacea, however the various biologically based therapies discussed herein should be considered as adjuncts for certain patients as part of a comprehensive, holistic management plan. In addition, patients should be counseled about home remedies that do not have evidence supporting their use, such as toothpaste, baking soda and diluted apple cider vinegar, which may cause irritation and chemical burns.[97]

DISCLOSURES

Jonette Keri MD PhD is a consultant to Hoffman-La Roche and an Advisory Board Member to Pierre Fabre and Ortho Dermatologics.

REFERENCES

1. US Department of Health and Human Services NIoH, National Cancer Institute, National Center for Complementary and Alternative Medicine. Thinking About Complementary & Alternative Medicine. [PDF]. https://www.cancer.gov/publications/patient-education/367NCINewV2.pdf. Accessed November, 2017.
2. Health NCfCaI. Complementary, Alternative, or Integrative Health: What's In a Name? [Webpage]. https://nccih.nih.gov/health/integrative-health - cvsa. Accessed November, 2017.
3. MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. Prev Med. 2002;35(2):166-173.
4. Integrative Dermatology. New York, NY: Oxford University Press.
5. Fuhrmann T, Smith N, Tausk F. Use of complementary and alternative medicine among adults with skin disease: updated results from a national survey. J Am Acad Dermatol. 2010;63(6):1000-1005.
6. Smith N, Shin DB, Brauer JA, Mao J, Gelfand JM. Use of complementary and alternative medicine among adults with skin disease: results from a national survey. J Am Acad Dermatol. 2009;60(3):419-425.
7. Magin PJ, Adams J, Heading GS, Pond DC, Smith W. Complementary and alternative medicine therapies in acne, psoriasis, and atopic eczema: results of a qualitative study of patients' experiences and perceptions. J Altern Complement Med. 2006;12(5):451-457.
8. Klock J, Ikeno H, Ohmori K, Nishikawa T, Vollhardt J, Schehlmann V. Sodium ascorbyl phosphate shows in vitro and in vivo efficacy in the prevention and treatment of acne vulgaris. Int J Cosmet Sci.

2005;27(3):171-176.
9. Spiclin P, Homar M, Zupancic-Valant A, Gasperlin M. Sodium ascorbyl phosphate in topical microemulsions. Int J Pharm. 2003;256(1-2):65-73.
10. Ruamrak C, Lourith N, Natakankitkul S. Comparison of clinical efficacies of sodium ascorbyl phosphate, retinol and their combination in acne treatment. Int J Cosmet Sci. 2009;31(1):41-46.
11. Woolery-Lloyd H, Baumann L, Ikeno H. Sodium L-ascorbyl-2-phosphate 5% lotion for the treatment of acne vulgaris: a randomized, double-blind, controlled trial. J Cosmet Dermatol. 2010;9(1):22-27.
12. Walocko FM, Eber AE, Keri JE, Al-Harbi MA, Nouri K. The role of nicotinamide in acne treatment. Dermatol Ther. 2017.
13. Draelos ZD, Matsubara A, Smiles K. The effect of 2% niacinamide on facial sebum production. J Cosmet Laser Ther. 2006;8(2):96-101.
14. Grange PA, Raingeaud J, Calvez V, Dupin N. Nicotinamide inhibits Propionibacterium acnes-induced IL-8 production in keratinocytes through the NF-kappaB and MAPK pathways. J Dermatol Sci. 2009;56(2):106-112.
15. Morganti P, Berardesca E, Guarneri B, et al. Topical clindamycin 1% vs. linoleic acid-rich phosphatidylcholine and nicotinamide 4% in the treatment of acne: a multicentre-randomized trial. Int J Cosmet Sci. 2011;33(5):467-476.
16. Dos SK, Barbhuiya JN, Jana S, Dey SK. Comparative evaluation of clindamycin phosphate 1% and clindamycin phosphate 1% with nicotinamide gel 4% in the treatment of acne vulgaris. Indian J Dermatol Venereol Leprol. 2003;69(1):8-9.
17. Sardesai VR, Kambli VM. Comparison of efficacy of topical clindamycin and nicotinamide combination with plain clindamycin for the treatment of acne vulgaris and acne resistant to topical antibiotics. Indian J Dermatol Venereol Leprol. 2003;69(2):138-139.
18. Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK. Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. Int J Dermatol. 1995;34(6):434-437.
19. Barros BS, Zaenglein AL. The Use of Cosmeceuticals in Acne: Help or Hoax? Am J Clin Dermatol. 2017;18(2):159-163.
20. Niren NM, Torok HM. The Nicomide Improvement in Clinical Outcomes Study (NICOS): results of an 8-week trial. Cutis. 2006;77(1 Suppl):17-28.
21. Shalita AR, Falcon R, Olansky A, et al. Inflammatory acne management with a novel prescription dietary supplement. J Drugs Dermatol. 2012;11(12):1428-1433.
22. Langner A, Sheehan-Dare R, Layton A. A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide (Duac) and erythromycin + zinc acetate (Zineryt) in the treatment of mild to moderate facial acne vulgaris. J Eur Acad Dermatol Venereol. 2007;21(3):311-319.
23. Dreno B, Amblard P, Agache P, Sirot S, Litoux P. Low doses of zinc gluconate for inflammatory acne. Acta Derm Venereol. 1989;69(6):541-543.
24. Habbema L, Koopmans B, Menke HE, Doornweerd S, De Boulle K. A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. Br J Dermatol. 1989;121(4):497-502.
25. Schachner L, Eaglstein W, Kittles C, Mertz P. Topical erythromycin and zinc therapy for acne. J Am Acad Dermatol. 1990;22(2 Pt 1):253-260.
26. Dreno B, Foulc P, Reynaud A, Moyse D, Habert H, Richet H. Effect of zinc gluconate on propionibacterium acnes resistance to erythromycin in patients with inflammatory acne: in vitro and in vivo study. Eur J Dermatol. 2005;15(3):152-155.

27. Sardana K, Garg VK. An observational study of methionine-bound zinc with antioxidants for mild to moderate acne vulgaris. Dermatol Ther. 2010;23(4):411-418.
28. Dreno B, Blouin E. [Acne, pregnant women and zinc salts: a literature review]. Ann Dermatol Venereol. 2008;135(1):27-33.
29. Hammer KA. Treatment of acne with tea tree oil (melaleuca) products: a review of efficacy, tolerability and potential modes of action. Int J Antimicrob Agents. 2015;45(2):106-110.
30. Armstrong AW, Cheeney S, Wu J, Harskamp CT, Schupp CW. Harnessing the power of crowds: crowdsourcing as a novel research method for evaluation of acne treatments. Am J Clin Dermatol. 2012;13(6):405-416.
31. Carson CF, Hammer KA, Riley TV. Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbiol Rev. 2006;19(1):50-62.
32. Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. Med J Aust. 1990;153(8):455-458.
33. Enshaieh S, Jooya A, Siadat AH, Iraji F. The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study. Indian J Dermatol Venereol Leprol. 2007;73(1):22-25.
34. de Groot AC, Schmidt E. Tea tree oil: contact allergy and chemical composition. Contact Derm. 2016;75(3):129-143.
35. Graham HN. Green tea composition, consumption, and polyphenol chemistry. Prev Med. 1992;21(3):334-350.
36. OyetakinWhite P, Tribout H, Baron E. Protective mechanisms of green tea polyphenols in skin. Oxid Med Cell Longev. 2012;2012:560682.
37. Yoon JY, Kwon HH, Min SU, Thiboutot DM, Suh DH. Epigallocatechin-3-gallate improves acne in humans by modulating intracellular molecular targets and inhibiting P. acnes. J Invest Dermatol. 2013;133(2):429-440.
38. Liao S. The medicinal action of androgens and green tea epigallocatechin gallate. Hong Kong Med J. 2001;7(4):369-374.
39. Li Z, Summanen PH, Downes J, et al. Antimicrobial Activity of Pomegranate and Green Tea Extract on Propionibacterium Acnes, Propionibacterium Granulosum, Staphylococcus Aureus and Staphylococcus Epidermidis. J Drugs Dermatol. 2015;14(6):574-578.
40. Mahmood T, Akhtar N, Khan BA, Khan HM, Saeed T. Outcomes of 3% green tea emulsion on skin sebum production in male volunteers. Bosn J Basic Med Sci. 2010;10(3):260-264.
41. Katiyar SK, Afaq F, Perez A, Mukhtar H. Green tea polyphenol (-)-epigallocatechin-3-gallate treatment of human skin inhibits ultraviolet radiation-induced oxidative stress. Carcinogenesis. 2001;22(2):287-294.
42. Elsaie ML, Abdelhamid MF, Elsaaiee LT, Emam HM. The efficacy of topical 2% green tea lotion in mild-to-moderate acne vulgaris. J Drugs Dermatol. 2009;8(4):358-364.
43. Taylor EJ, Yu Y, Champer J, Kim J. Resveratrol Demonstrates Antimicrobial Effects Against Propionibacterium acnes In Vitro. Dermatol Ther. 2014;4(2):249-257.
44. Kim SY, Hyun MY, Go KC, Zouboulis CC, Kim BJ. Resveratrol exerts growth inhibitory effects on human SZ95 sebocytes through the inactivation of the PI3-K/Akt pathway. Int J Mol Med. 2015;35(4):1042-1050.
45. Fabbrocini G, Staibano S, De Rosa G, et al. Resveratrol-containing gel for the treatment of acne vulgaris: a single-blind, vehicle-controlled, pilot study. Am J Clin Dermatol. 2011;12(2):133-141.

46. Rasheed A, Avinash Kumar Reddy G, Mohanalakshmi S, Ashok Kumar CK. Formulation and comparative evaluation of poly herbal anti-acne face wash gels. Pharm Biol. 2011;49(8):771-774.
47. Liu CH, Huang HY. In vitro anti-propionibacterium activity by curcumin containing vesicle system. Chem Pharm Bull. 2013;61(4):419-425.
48. Shuto T, Ono T, Ohira Y, et al. Curcumin decreases toll-like receptor-2 gene expression and function in human monocytes and neutrophils. Biochem Biophys Res Commun. 2010;398(4):647-652.
49. Lalla JK, Nandedkar SY, Paranjape MH, Talreja NB. Clinical trials of ayurvedic formulations in the treatment of acne vulgaris. J Ethnopharmacol. 2001;78(1):99-102.
50. Bowe WP, Joshi SS, Shalita AR. Diet and acne. J Am Acad Dermatol. 2010;63(1):124-141.
51. Smith RN, Mann NJ, Braue A, Makelainen H, Varigos GA. A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial. Am J Clin Nutr. 2007;86(1):107-115.
52. Smith RN, Mann NJ, Braue A, Makelainen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. J Am Acad Dermatol. 2007;57(2):247-256.
53. Kwon HH, Yoon JY, Hong JS, Jung JY, Park MS, Suh DH. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. Acta Derm Venereol. 2012;92(3):241-246.
54. Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. J Am Acad Dermatol. 2005;52(2):207-214.
55. Adebamowo CA, Spiegelman D, Berkey CS, et al. Milk consumption and acne in teenaged boys. J Am Acad Dermatol. 2008;58(5):787-793.
56. Bowe WP, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis - back to the future? Gut Pathog. 2011;3(1):1.
57. Volkova LA, Khalif IL, Kabanova IN. [Impact of the impaired intestinal microflora on the course of acne vulgaris]. Klin Med. 2001;79(6):39-41.
58. Jung GW, Tse JE, Guiha I, Rao J. Prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of an acne treatment regimen with and without a probiotic supplement and minocycline in subjects with mild to moderate acne. J Cutan Med Surg. 2013;17(2):114-122.
59. Kang BS, Seo JG, Lee GS, et al. Antimicrobial activity of enterocins from Enterococcus faecalis SL-5 against Propionibacterium acnes, the causative agent in acne vulgaris, and its therapeutic effect. J Microbiol. 2009;47(1):101-109.
60. Gehring W. Nicotinic acid/niacinamide and the skin. J Cosmet Dermatol. 2004;3(2):88-93.
61. Wozniacka A, Wieczorkowska M, Gebicki J, Sysa-Jedrzejowska A. Topical application of 1-methylnicotinamide in the treatment of rosacea: a pilot study. Clin Exp Dermatol. 2005;30(6):632-635.
62. Christman JC, Fix DK, Lucus SC, et al. Two randomized, controlled, comparative studies of the stratum corneum integrity benefits of two cosmetic niacinamide/glycerin body moisturizers vs. conventional body moisturizers. J Drugs Dermatol. 2012;11(1):22-29.
63. Draelos ZD, Ertel K, Berge C. Niacinamide-containing facial moisturizer improves skin barrier and benefits subjects with rosacea. Cutis. 2005;76(2):135-141.
64. Nicomide® Supplement Facts. http://www.nicomide.com/supplement-facts/nicomide-supplement-fact-sheet. Accessed March, 2018.
65. Baumann L, Woolery-Lloyd H, Friedman A. “Natural” ingredients in cosmetic dermatology. J Drugs

Dermatol. 2009;8(6 Suppl):s5-9.
66. Sur R, Martin K, Liebel F, Lyte P, Shapiro S, Southall M. Anti-inflammatory activity of parthenolide-depleted Feverfew (Tanacetum parthenium). Inflammopharmacology. 2009;17(1):42-49.
67. Martin K, Sur R, Liebel F, et al. Parthenolide-depleted Feverfew (Tanacetum parthenium) protects skin from UV irradiation and external aggression. Arch Dermatol Res. 2008;300(2):69-80.
68. Wu J. Treatment of rosacea with herbal ingredients. J Drugs Dermatol. 2006;5(1):29-32.
69. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res. 1998;11(6):355-361.
70. Weber TM, Ceilley RI, Buerger A, et al. Skin tolerance, efficacy, and quality of life of patients with red facial skin using a skin care regimen containing Licochalcone A. J Cosmet Dermatol. 2006;5(3):227-232.
71. Kolbe L, Immeyer J, Batzer J, et al. Anti-inflammatory efficacy of Licochalcone A: correlation of clinical potency and in vitro effects. Arch Dermatol Res. 2006;298(1):23-30.
72. Lee SH, Heo Y, Kim YC. Effect of German chamomile oil application on alleviating atopic dermatitis-like immune alterations in mice. J Vet Sci. 2010;11(1):35-41.
73. Merfort I, Heilmann J, Hagedorn-Leweke U, Lippold BC. In vivo skin penetration studies of camomile flavones. Die Pharm. 1994;49(7):509-511.
74. Rigopoulos D, Kalogeromitros D, Gregoriou S, et al. Randomized placebo-controlled trial of a flavonoid-rich plant extract-based cream in the treatment of rosacea. J Eur Acad Dermatol Venereol. 2005;19(5):564-568.
75. Domingo DS, Camouse MM, Hsia AH, et al. Anti-angiogenic effects of epigallocatechin-3-gallate in human skin. Int J Clin Exp Pathol. 2010;3(7):705-709.
76. Elmets CA, Singh D, Tubesing K, Matsui M, Katiyar S, Mukhtar H. Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. J Am Acad Dermatol. 2001;44(3):425-432.
77. Farris PK. Topical vitamin C: a useful agent for treating photoaging and other dermatologic conditions. Dermatol Surg. 2005;31(7 Pt 2):814-817; discussion 818.
78. Fowler JF, Jr., Woolery-Lloyd H, Waldorf H, Saini R. Innovations in natural ingredients and their use in skin care. J Drugs Dermatol. 2010;9(6 Suppl):S72-81; quiz s82-73.
79. Lin JY, Selim MA, Shea CR, et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. J Am Acad Dermatol. 2003;48(6):866-874.
80. Lin FH, Lin JY, Gupta RD, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. J Invest Dermatol. 2005;125(4):826-832.
81. Lim HW, Arellano-Mendoza MI, Stengel F. Current challenges in photoprotection. J Am Acad Dermatol. 2017;76(3s1):S91-s99.
82. Middelkamp-Hup MA, Pathak MA, Parrado C, et al. Oral Polypodium leucotomos extract decreases ultraviolet-induced damage of human skin. J Am Acad Dermatol. 2004;51(6):910-918.
83. Kohli I, Shafi R, Isedeh P, et al. The impact of oral Polypodium leucotomos extract on ultraviolet B response: A human clinical study. J Am Acad Dermatol. 2017;77(1):33-41.e31.
84. Elewski BE, Draelos Z, Dreno B, Jansen T, Layton A, Picardo M. Rosacea - global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. J Eur Acad Dermatol Venereol 2011;25(2):188-200.
85. Kligman AM. A personal critique on the state of knowledge of Rosacea. Dermatology. 2004;208(3):191-197.
86. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent

findings. J Am Acad Dermatol. 2013;69(6 Suppl 1):S15-26.
87. Kamanna VS, Ganji SH, Kashyap ML. The mechanism and mitigation of niacin-induced flushing. Int J Clin Pract.. 2009;63(9):1369-1377.
88. Sullivan BD, Cermak JM, Sullivan RM, et al. Correlations between nutrient intake and the polar lipid profiles of meibomian gland secretions in women with Sjogren's syndrome. Adv Exp Med Biol. 2002;506(Pt A):441-447.
89. Miljanovic B, Trivedi KA, Dana MR, Gilbard JP, Buring JE, Schaumberg DA. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr. 2005;82(4):887-893.
90. Kronemyer B. Dry eye successfully treated with oral flaxseed oil. 2000; https://www.healio.com/ophthalmology/news/print/ocular-surgery-news-europe-asia-edition/%7B4f2c5812-13f1-4b41-abaf-d1d5cf12bed9%7D/dry-eye-successfully-treated-with-oral-flaxseed-oil, 2017.
91. Jones SM, Weinstein JM, Cumberland P, Klein N, Nischal KK. Visual outcome and corneal changes in children with chronic blepharokeratoconjunctivitis. Ophthalmology. 2007;114(12):2271-2280.
92. Bhargava R, Chandra M, Bansal U, Singh D, Ranjan S, Sharma S. A Randomized Controlled Trial of Omega 3 Fatty Acids in Rosacea Patients with Dry Eye Symptoms. Curr Eye Res. 2016;41(10):1274-1280.
93. Parodi A, Paolino S, Greco A, et al. Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. Clin Gastroenterol Hepatol. 2008;6(7):759-764.
94. Weinstock LB, Steinhoff M. Rosacea and small intestinal bacterial overgrowth: prevalence and response to rifaximin. J Am Acad Dermatol. 2013;68(5):875-876.
95. Riordan SM, McIver CJ, Thomas DH, Duncombe VM, Bolin TD, Thomas MC. Luminal bacteria and small-intestinal permeability. Scand J Gastroenterol. 1997;32(6):556-563.
96. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut. 2015;64(1):93-100.
97. Mill J, Wallis B, Cuttle L, Mott J, Oakley A, Kimble R. Phytophotodermatitis: case reports of children presenting with blistering after preparing lime juice. Burns. 2008;34(5):731-733.

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