

Acne Supplementation: Probiotics, Vitamins, and Diet

Camilla Chello¹, Claudio Conforti², Caterina Dianzani¹

¹Dermatology Section, Department of Plastic, Reconstructive and Cosmetic Surgery, "Campus Bio-medico" University, Rome, Italy; ²Dermatology Clinic, Maggiore Hospital, University of Trieste, Trieste, Italy

Corresponding author:

Camilla Chello, MD
Università Campus Bio-Medico di Roma
Via Álvaro del Portillo 200
00128 Roma
Italy
camilla.chello@gmail.com

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ABSTRACT Acne is an inflammatory disease of the pilo-sebaceous unit, which mainly affects young adolescents. The pathogenesis is multifactorial, as a combination of genetic predisposition, hormonal production, hyper-seborrhea, inflammation and overgrowth of *C. acnes*. Moreover, diet-induced hyperinsulinemia can lead to sebocyte stimulation, androgen production, and thus acne lesions. Pharmacological therapeutic approaches are varied and include topical and systemic antibiotics and, in severe cases, systemic retinoids, with several side-effects. However, increasing evidence has shown that adequate vitamin supplementation, use of probiotics, and proper nutrition with low carbohydrates and fats intake, can significantly contribute to the patient's clinical improvement. In this review, we describe the role of probiotics, vitamins, alimentation, antioxidants, UV exposure, and plants in acne disease.

KEY WORDS: acne, vitamins, diet, probiotics

INTRODUCTION

Acne is an inflammatory disease of the pilosebaceous unit, mainly affecting the adolescent population with a prevalence that can peak to 87%, and less frequently also affecting adult patients. The pathogenesis is multifactorial, including a state of hyperseborrhea, hormonal production, inflammation and overgrowth by *Cutibacterium acnes* (1).

Clinical manifestations are variable, from papular lesions in the mild form, papular-pustular in the moderate form and nodulocystic lesions in the severe form. Moreover, acute-phase lesions may leave aesthetically disabling scars, leading to psychological repercussions with loss of self-confidence, social distancing, and isolation. The different therapeutic options currently available, mainly antibiotics and vitamin A derivatives (retinoids), are not free from side-effects, which in turn reduce patient compliance to therapy.

Recent evidence shows that proper diet and vitamin supplementation adjunct to the pharmacological treatment might provide an important contribution in clinical improvement of acne lesions. Notably, the role of the microbiome, both intestinal and cutaneous, has been deeply investigated in recent studies.

In this context, the concept of the exposome has been introduced in 2005, which considers all the external factors affecting the patient from birth until death and includes exposure to UV radiation, smog, nutrition, and the psychological environment. As a consequence, the exposome affects all areas of an individual's life, impacting up to 60% on chronic diseases (1).

The skin, due to its characteristics as a physical, chemical, and immunological barrier, represents an ideal study model; the role of the exposome, in fact, has already been studied in the pathogenesis of skin

aging, and a recent study evaluated the influence of nutrition, climate, environmental pollution, and psychological factors on acne development (1).

The aim of this narrative review is to investigate the role of dysbiosis (use of topical and oral probiotics), nutrition, antioxidants, vitamins, plants, and environmental factors in the pathogenesis of acne disease.

DISBYOSIS

One of the first clinical studies carried out in 1930 (2) to evaluate the correlation between gastro-intestinal alterations and skin manifestations found a state of hypochloridia in 40% of patients with acne: this condition might affect intestinal permeability, promoting bacterial growth and leading to a state of inflammation. The rationale of this association lies in the increased intestinal permeability found in patients with acne, which would favor the entry of pathogens (3). Indeed, gut microbiota modulate the host immunological response and, in case of intestinal barrier disruption, gut microorganisms are released into the bloodstream and reach the skin, where they interact with resident flora, thus causing an alteration of local homeostasis.

Moreover, gut metabolites may activate the mTOR pathway, which is known to be involved in the pathogenesis of acne (4).

PROBIOTICS AND ACNE

The skin microbiome is a complex ecosystem that regulates skin homeostasis, contributing to barrier integrity. Back in 1912, a therapy that targeted the microbiome was employed, particularly the use of *Lactobacillus bulgaricus* in acne, resulting in reduced seborrhea (5). The effect of topical probiotics seems to regulate the immune response, reducing the inflammatory state and promoting the production of anti-inflammatory cytokines such as IL-10 (6). In particular, lactobacilli seem to have an antibacterial action against *C. acnes*. However, it should be noted that each species has specific characteristics and that the transposition of a strain to a receiving site could

lead to an altered function of the strain. Several studies have shown the peculiarity of the microbiome in patients with acne and that its modulation can lead to significant clinical results. In a Russian study involving 144 patients, differences in intestinal bacterial flora were found in patients with acne (7); when treated with probiotics, the duration of classical pharmacological treatment was reduced among these patients.

TOPICAL PROBIOTICS

In the field of topical probiotics, a recent study experimented on the use of polysulfone microtube array membrane (MTAM) to encapsulate *S. epidermidis* (8). Murine models were subjected to the action of *C. acnes*, and then the topical formulation of membranes with encapsulated *S. epidermidis* plus glycerol was applied. This formulation was effective in increasing the fermentation activity of glycerol, with reduction of *C. acnes* and inflammation, through the action of succinic acid (8).

In vitro studies have demonstrated the ability of *S. epidermidis* and *E. fecalis* to directly inhibit *C. acnes* growth through the production of antibacterial proteins, including a bacteriocin-like inhibitory substance (BLIS) (9,10). Another *in vitro* study by Wang showed that *S. epidermidis* is able to ferment glycerol to form short-chain fatty acids that inhibit *C. acnes* growth (11).

In 2016, the same author published a paper in which he used sucrose instead of glycerol, as it has the ability to selectively promote the fermentation of *S. epidermidis*, but not *C. acnes* (12): the design of the study consisted in an injection of both *C. acnes* and *S. epidermidis* into the ears of murine models, to which either sucrose or phosphate buffered saline was added (PBS). The results showed a reduced growth of the pathogen as well as the production of macrophage-inflammatory protein-2 (MIP-2) in the group in which sucrose was added.

Streptococcus salivarius is also able to inhibit, *in vitro*, the growth of *C. acnes* through the production of BLIS (13,14), which has the ability to modulate the inflammatory response. Another *in vitro* study showed

Table 1. Acne: non pharmacological interventions

Intervention	Mechanism of action
Diet	Low fat and milk-derivatives daily intake
UV exposure	Use sun protection to avoid UV-related immunological effects
Vitamin assumption	Favor vitamin D, C, E intake
Omega-3 and 6	Prefer fish-rich diet to increase anti-inflammatory effects of Omega-3 and 6
Probiotics	Use of topical and oral probiotics may improve gut and skin Microbiome, limiting <i>C. acnes</i> overgrowth

the production of a bactericidal substance (against several pathogens including *C. acnes*) by *Lactococcus sp. HY 449* (15); furthermore, this substance would not have irritating phenomena, as confirmed by a PATCH test carried out with the same product: these characteristics raised the possibility of using it in cosmetic products as an antimicrobial agent.

In 2009, another study on direct antimicrobial effects against *C. acnes* by *Enterococcus faecalis SL-5* (16) was published. The randomized, double-blind clinical trial evaluated the effects of twice-daily application of a lotion containing *E. faecalis SL-5* versus placebo in patients with mild to moderate acne at 2, 4, and 8 weeks, with significant reduction of lesions in the treated group. Another clinical study evaluated the efficacy of *Lactobacillum plantarum* in 1% topical formulations, 5% vs 1% salicylic acid in 10 volunteers, with a significant reduction in lesions and erythema in the 5% formulation (17).

ORAL PROBIOTICS

In addition to the possibility of topical formulations, the effects of oral probiotics in acne have also been extensively investigated. A clinical study assessed the effectiveness of daily administration of fermented milk enriched with 200 mg lactoferrin for 12 weeks, noting a reduction in inflammatory lesions in 38.6% of patients (18). Another clinical study reported the effectiveness of a mix of probiotics composed of *Lactobacillus acidophilus* (NAS super-strain), *Lactobacillus delbrueckii subspecies bulgaricus* (LB-51 super-strain), and *bifidobacterium bifidum* on 45 women divided into three groups: one treated with probiotics only, one treated with minocycline only, and one treated with both of them (19). Reduction of total lesion count as well as in inflamed lesions was significantly evident in group treated with minocycline and probiotics (week 8 and 12), while clinical improvement was observed in all groups. Moreover, the group treated with a combination of minocycline and probiotics achieved a significant improvement early at week 4 and continued to improve. At weeks 4, 8, and 12, the probiotic-only group showed a greater reduction in non-inflamed lesions compared with the minocycline-only group (19).

In 2016, a study coordinated by Prof. Fabbrocini showed that oral supplementation with *Lactobacillus rhamnosus SP1* for a period of 12 weeks resulted in a reduction of cutaneous expression of IGF-1 and FOXO1 (20). At the end of 12 weeks, the group of patients treated with oral supplementation of *L. rhamnosus* showed 32% ($P<0.001$) reduction in the expression of IGF1-encoding genes and a 65% ($P<0.001$)

increase in those coding for FOXO1, while there were no statistically significant differences in the placebo group.

Key points:

Probiotics have several immunoregulatory roles.

They reduce inflammation and promote secretion of anti-inflammatory cytokines, such as IL-10.

They inhibit *C. acnes* overgrowth, stimulating the production of bacteriocin-like inhibitory substance (BLIS).

Oral supplementation may reduce skin expression of comedogenic molecules, IGF-1, and FOXO.

VITAMIN D

Vitamin D has an immunoregulatory effect, and its deficiency has also been found in other skin conditions such as atopic dermatitis and psoriasis. It is able to inhibit the production of proinflammatory cytokines such as IL-6, IL-8, and the Th17 shift mediated by *C. acnes* (21).

It also inhibits the production of IFN-induced proinflammatory cytokines in monocytes (IL-1, IL-6, TNF- α , IL-8, and IL-12), the proliferation of T-lymphocytes, and the shift to Th1 (22). Moreover, vitamin D has antimicrobial effects, stimulating the production of LL37 in sebocytes (vitamin D receptors were found in these cells).

Vitamin D also supports the production of important antioxidant agents, such as GSH-px (glutathione peroxidase) and superoxide dismutase (SOD), which are reduced in patients with papulopustular acne (23).

Given its multiple effects in the immunological response, some studies have evaluated the possible interaction between serum vitamin D levels and acne disease (22).

A 2016 study assessed the possible correlation between acne and vitamin D levels (24). Serum levels of (25(OH)D) were evaluated in 80 patients with acne and 80 controls, and a vitamin D deficiency was found in 48.8% of patients with acne compared with 22.5% of controls; in particular, a significant inverse correlation ($r=0.512$; $P<0.001$) was found between the degree of deficiency and severity of disease (number of inflammatory lesions).

In addition, oral supplementation was administered in patients with deficiency, which resulted in improvement in 39 patients, with significant concomitant improvement in inflammatory lesions ($P<0.05$).

However, several studies showed contradictory results. In a recent clinical trial, 714 patients were

examined for both serum vitamin D levels and clinical assessment of acne, but no statistically significant correlations were found between the two variables, even after adjustment for possible confounding bias (22). The authors explained this apparently contradictory result by emphasizing i) the non-uniform distribution of serum vitamin D in their cohorts; ii), that the patients in the study predominantly had mild-moderate acne, thus excluding the more severe forms in which this correlation could actually be observed.

VITAMIN B12

Biosynthesis of this vitamin in *C. acnes* is reduced in patients with acne. There are several studies in the literature reporting pharmacological acne induced by Vitamin B12 intake (25,26). In particular, a recent clinical study assessed the correlation between B12 and acne, supplementing the microbiota of healthy subjects with B12 (26). Supplementation resulted in a suppression of the expression of the genes involved in the biosynthesis of vitamin B12 in *C. acnes*, altering the transcriptome of the skin microbiota.

In addition, one of the healthy subjects in the study developed acne after vitamin supplementation. To better clarify the correlation between vitamin B12 and acne, *C. acnes* cultures were supplemented with B12, resulting an increased production of porphyrins, with induction of an inflammatory state in acne (26).

Finally, an important issue in patients with severe acne is that treatment with oral isotretinoin may induce hyper-homocysteine levels and reduction in folic acid and vitamin B12 levels, increasing cardiovascular and neuropsychiatric risks.

A significant correlation has also been described between cumulative retinoid doses and folate reduction. The exact underlying mechanism is not known, and a reduction in vitamin absorption has been hypothesized (27).

ZINC

Zinc is a divalent cation with a relevant role in the activity of enzymes and transcription factors and required in the regulation of lipids and proteins (28). It modulates the action of the immune system, the production of pro-inflammatory cytokines, and has antioxidant properties. In particular, it reduces neutrophil chemotaxis, Th17 activation, and TLR2 expression from keratinocytes (29-31). It also appears to be bacteriostatic and inhibits chemotaxis of pro-inflammatory cytokines, including TNF- α (30). Several studies evaluated the efficacy of zinc supplementation in the treatment of acne as well as zinc and methionine

compounds with antioxidants in patients with mild-to-moderate acne. In a review from 2019, zinc use as supplementation in various skin conditions was reported (31). Out of 22 articles, 14 reported the use of zinc in acne with beneficial results.

Some studies compared zinc with placebo, antibiotics, and vitamin A, with differing results. In fact, while some authors reported a clinical improvement of acne lesions in patients treated with zinc, compared with those treated with placebo, other studies found a reduced efficacy of zinc alone compared with antibiotics (31).

The most frequent side-effect of zinc is related to gastrointestinal disorders, nausea, and vomiting; these complications often reduce patient compliance for zinc supplements. Zinc is bacteriostatic against *C. acnes*: it is able to reduce the production of IGF-1 and its receptor, facilitates the conversion of retinol to retinoic acid, increases the synthesis of retinol binding protein, inhibits 5 α reductase, and inhibits neutrophil chemotaxis (32).

ALIMENTATION

The association between acne and nutrition has been extensively investigated. Some foods have been investigated in acne pathogenesis, especially milk and dairy products and a diet rich in carbohydrates.

A study published in 2018 by Cutis looked at what the most frequent Google searches on diet and skin conditions, including acne (33). Most sites recommended a diet low in high-glycemic foods and dairy products, favoring the intake of Omega-3 and foods with antioxidant properties. A study on 2258 patients found that a low glucose diet was associated with a significant reduction in lesions (87%) and, consequently, the use of specific medications (91%). In a study published in 2007 (34), male patients with moderate to severe acne had a low-carbohydrate diet for a total of 12 weeks, with measurements of sex hormone levels, insulin levels at baseline and at the end of the diet, as well as a clinical evaluation of the lesions both at baseline and at the end of the study. Researchers observed a reduction in the number of lesions and serum levels of the above markers, confirming the thesis that a good diet can contribute to clinical improvement.

Given the correlation between acne and a state of insulin resistance and metabolic syndrome, it seems intuitive to think that nutrition can be a determining factor. Elevated IGF results in increased androgen synthesis and incremented action on mTOR receptors (35). In a case-control study in young people aged 10-24, milk intake of more than three servings per

week was associated with an increased risk of moderate-severe acne; the strongest combination was observed for skim milk, while the consumption of fish appeared to be protective (32).

Insulin levels are known to favor acne. In fact, patients with PCOS also present acne lesions, among the various clinical manifestations. In this case, hyperinsulin levels would promote an increase in IGF-1 with increased proliferation of keratinocytes and hormone levels.

IGF-1 stimulates androgen receptors through the action of 5 α reductase, with stimulation of keratinocytes, sebocytes, and increased lipogenesis (30,36). In particular, milk induces an increase in insulin levels; additionally, cow's milk contains reduced androgens 5 α (5 α -pregnanedione, 5 α -androstanedione), which pass from the cow's placenta into the milk (37). Milk also contains the bovine form of IGF-1, which has similar characteristics to that of humans. These characteristics may explain the elevated incidence of acne in patients who use milk and dairy products frequently.

Key points:

Carbohydrates, milk, and dairy product may increase acne development.

They promote hyperinsulinemia.

Hyperinsulinemia stimulates IGF-1 production, which in turn increase androgen levels, with stimulation of keratinocytes and sebocytes, thus increasing lipogenesis.

Cow's milk 5 α reduced androgens and the bovine form of IGF-1.

PLANTS AND ACNE

Polyphenols are naturally found in fruits and vegetables. They have the ability to reduce the absorption of glucose in the gut, acting on insulin sensitivity (33). In a 2016 randomized clinical trial, green tea supplementation reduced the number of acne lesions in adolescent female patients with reduced glucose levels (38).

Among the other plants that have been studied, Berberine seems to be able to act on insulin resistance at the level of the hepatocytes and seems to have antimicrobial activity against *C. acnes* (33). A study carried out with the fruit supplement of Mahonia, belonging to the same family as Berberine, demonstrated efficacy in the group of patients treated with fruit supplement almost comparable to that in patients treated with minocycline (39).

Sexual hormones also play a role in the pathogenesis of acne; in particular, circulating testosterone levels appear to be responsible for acne lesions.

Phytoestrogens are present in various herbs, particularly soya, in the form of isoflavonoids. In particular, there are several polyphenols within vitex-agnus-castus which, acting on FSH and LH, would stimulate progesterone production (40).

Additionally, the root of curcuma longa and azadirachta indica appear to have an anti-inflammatory effect by suppressing the production of pro-inflammatory cytokines and ROS induced by *C. acnes* (33). Gugulipid is a derivative of the commiphora mukul tree already used in Chinese medicine for its anti-inflammatory activities. In a clinical study in patients with nodulocystic acne treated with either gugulipid or tetracycline, a reduction in lesions was shown in both groups ($P>0.05$) (41).

Tea tree oil is derived from crushing the leaves the melaleuca tree and is used in various pathological conditions due to its properties. In acne, it appears to possess anti-inflammatory and antibacterial properties acting on *C. acnes* (35). Several studies have assessed the effectiveness of tea tree oil in acne disease, including studies in the pediatric population (35). These studies found an improvement in lesions compared with control groups, although the treatment used in these groups varied between studies.

Berberis vulgaris is a plant from which we derive berries (berberries) (35). They appear to have anti-inflammatory, antioxidant, and antimicrobial properties. A randomized double-blind clinical study assessed the efficacy of tablets containing berry extracts in patients with moderate to severe acne (42), and the results showed a reduction in the number of lesions after four weeks of treatment.

OMEGA-3 AND 6

Omega-3 and 6 as well as polyunsaturated fatty acids are important components of human metabolism and derived from food, with fish oil and plants as the main source. Among them, linoleic acid (Omega-6) and alpha linoleic acid (Omega-3) are called essential fatty acids. They have different functions: they are involved in gene expression, lipid composition of membranes, and cellular metabolism (43). Moreover, Omega-3 and 6 fatty acids have important anti-inflammatory properties and since the inflammatory process may play a pivotal role in the clinical scenario of acne, it is thus intuitive that the intake of such fatty acids can be beneficial.

A diet rich in fiber and omega fatty acids seems to reduce the risk of developing acne lesions. In particular, omega-3 and 6 can inhibit the inflammatory process and the production of leukotrienes, which play an important role in the production of sebum (30).



C. acnes can stimulate TLR expression on keratinocytes and macrophages; however, Omega-3 inhibits transduction signal by blocking TLR dimerization and consequent pro-inflammatory cytokine cascade. They are also able to inhibit the production of IL-1 β and the activation of the NF- κ B pathway, reducing serum IGF-1 levels (43).

Several studies found that a diet rich in fish containing large amounts of Omega-3 resulted in a less oily skin with fewer acne lesions, while other studies conducted in patients with acne showed a reduction in inflammatory and non-inflammatory lesions (43).

In addition, studies in patients treated with oral isotretinoin and who developed subsequent cheilitis showed that supplementation of fatty acids such as gamma-linoleic acid (GLA) improved excessive retinoid-induced dryness (44).

Confirm the protective and restorative role of Omega-3 in the skin barrier, a study in 118 patients with moderate-severe acne showed that the group taking Omega-3 fatty acid supplementation had less mucosal effects induced by retinoids (45).

ANTIOXIDANTS AND VITAMIN A

When considering the inflammatory course of acne, it is important to evaluate the efficacy of antioxidant substances. Several studies have found a low concentration of antioxidants in the plasma of patients with acne (Vitamin A and E), as well as selenium, which is important for glutathione peroxidase activity (30). In particular, a clinical study conducted on women with acne who received supplementation with vitamin E and selenium, found that lesions were reduced after 12 weeks of treatment (46). Even catechins and nobiletin seem to act on the regulation of sebum production (30). Finally, resveratrol not only possesses antioxidant properties but also appears to be bactericidal against *C. acnes*.

Vitamin A is a fat-soluble molecule whose main source are plants rich in carotenoids (vitamin A derivatives), such as sweet potatoes and carrots. Once ingested, Vitamin A is converted into its metabolites, retinoids, which exert their effects on skin through their nuclear receptors (RAR), making them a therapeutic option for different skin diseases. In particular, retinoids are used in acne due to their keratolytic and immunomodulatory effects and the modulation of cell proliferation (47).

Several studies have demonstrated the ability of *C. acnes* to induce Th1 (IFN- γ) and Th17 response; the latter is able to produce IL-17 and ROR (retinoic orphan receptors), Ror a and Ror c. They further induce

an inflammatory cascade which is responsible for clinical damage (48).

Vitamin A as well as vitamin D use the same receptor (RXR) for retinoids, through which they inhibit the production Th17-related cytokines.

In vitro studies have shown that the administration of both vitamin A and vitamin D is able to block cytokine production induced by *C. acnes* (48).

UV RADIATION

The role of ultraviolet radiation in the pathogenesis of skin lesions is well-known and is mainly mediated by DNA damage in the formation of reactive oxygen species (ROS), which cause lipid and protein peroxidation with consequent functional damage.

Specifically, UV-A and UV-B induce sebaceous hyperplasia, with increased sebum production, thickening of the stratum corneum, and increased number of comedones. UV radiation also stimulates the activation of the innate immunological response and suppress the adaptive one (1), resulting in skin environment damage, which could therefore promote *C. acnes* growth.

In addition, UV radiation is able to oxidize squalene, which represents 10-15% of sebum composition: the peroxidation of squalene is comedogenic and pro-inflammatory (49); moreover, a high concentration of squalene promotes the formation of ROS, which are actually elevated in patients with acne. Finally, UV radiation appears to have an additive effect on the harmful (pro-inflammatory) effects mediated by the pollutants present in the air.

However, the effects of UV radiation also depend on their wavelength. If UV-B rays are responsible for the damage described above, it appears that 400 nm UV-A may have anti-inflammatory effects in patients with acne (50). At the same time, it seems that blue radiation (420 nm wavelength) has anti-inflammatory effects on keratinocytes, being able to inhibit cytokine production, specifically IL-1 α and ICAM-1 (51).

CONCLUSION

Acne is a multifactorial disease, and it is important to consider all the elements that, combined together, determine its pathology. Proper nutrition, with a diet rich in vegetables and low in carbohydrates and fats can improve the metabolic status of the patient, reduce inflammatory processes and consequently clinical lesions, and should be used together with adequate vitamin supplementation, thanks to immunological and antioxidant properties of vitamin D, E, and A (Table 1).

The above-mentioned measures, together with limiting exposure to external triggers, mainly UV and pollution, may contribute to the resolution of the clinical picture, thus reducing the need for more aggressive pharmacological treatments and exposure to their side-effects.

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