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A Plan for Nutraceutical/Dietary Management of Acne Targeting De Novo Lipogenesis and Inflammation

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Abstract

The pathogenesis of acne involves an excess of sebum production. Sebum is a fatty substance produced by de novo lipogenesis (DNL) in sebocytes. A key driver of DNL is the transcription factor steroid response element-binding protein 1-c (SREBP-1c), promoted by insulin-like growth factor-1 (IGF-1)-mediated activation of Akt. Akt disinhibits the LXR-mediated transcription of the SREBP-1c gene by promoting nuclear exclusion of FOXO1; concurrently, it promotes proteolytic activation SREBP-1c, while enhancing its half-life, via mTORC1-p70 S6 kinase signaling. Adenosine 5'-monophosphate-activated protein kinase (AMPK) can oppose SREBP-1c activity by suppressing LXR expression, while also inhibiting mTORC1; in addition, it also opposes DNL via direct inhibition of acetyl-coA carboxylase 1 (ACC1). Sirtuin 1 (Sirt1) inhibits the transactivational activity of SREBP-1c by deacetylating it, and also boosts AMPK activity. It is proposed that nutraceuticals which activate AMPK (such as berberine) and Sirt1 (such as ferulic acid, methylnicotinamide, and melatonin) thus inhibiting sebocyte DNL. Bacterially driven inflammation may be suppressed with nutraceutical antioxidants such as spirulina, lipoic acid, N-acetylcysteine, and supplemental fish oil. Dietary wise, the plasma free IGF-1 which promotes sebocyte DNL could be reduced with low-protein plant-based diets or low-glycemic-load "Paleolithic" diets, consistent with the observation that acne is a "disease of civilization". ***Practical Applications:*** *The present review is focused on feasible nutraceutical strategies for Acne therapy targeting de novo lipogenesis and inflammation. The topic of nutraceuticals that down-regulate those two major pathological pathways in Acne development is a new evolving therapeutical strategy. The mechanisms are reported, and the different nutraceuticals interact in a complementary fashion to reduce risk of Acne, while also helping to prevent it. Additionally, the present review reports practical daily dose ranges for those nutraceuticals that might be expected to have physiological activity. To our knowledge, such an updated manuscript, on the topic of Acne and nutraceuticals is not available in the food or medical literature.*

Keywords: Nutraceuticals, acne, dietary management, sebocyte, steroid response element-binding protein 1-c, insulin-like growth factor-I, low Glycemic Index Paleolithic Diet, low-protein plant-based diet, berberine, ferulic acid

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INTRODUCTION

Acne, also known as acne vulgaris, is a common, long-term, puberty-associated skin condition that occurs when necrotic skin cells and oil from the skin clog pilosebaceous units. This creates an environment suitable for bacterial infection, which in turn triggers inflammation. As a hormone-dependent disorder whose geo-epidemiological distribution is higher in developed countries, it might be classified as a "disease of civilization" [1]. This epidemiology has encouraged speculation that dietary factors may be drivers of acne pathogenesis.

The following narrative review provides an update on the potential of nutraceuticals and optimal dietary choices for aiding prevention and treatment of acne, with a focus on amelioration of sebum over-production and bacterially induced inflammation. It does not intend to cover the topic of dermatological anti-inflammatory, nor anti-lipogenic agents used to alleviate acne, hence, concentrates on potential mechanisms by which nutraceuticals could diminish acne associated *de novo* lipogenesis and inflammation.

ACNE IN A NUTSHELL

Worldwide, the overall age-standardized prevalence of acne vulgaris has increased by approximately 0.55% per year over last three decades. Its prevalence continues to increase in most countries [2]. It affects around 80–90% of teenagers in the Western world, most notably in industrialized areas. Pre-pubertal children and young adults may also be affected, and acne may persist in nearly half of affected people into their 20s and 30s. Clinically, the typical skin lesions include whiteheads or blackheads, oily skin, and pimples, that may progress to cutaneous scarring. Skin regions with relatively higher numbers of oil glands, including the face, back and upper part of the chest, are primarily affected. This condition can be associated with reduced self-esteem owing to its potentially adverse impact on interpersonal relations, leading in some cases to affective disorders such as anxiety and depression. A twin study found that 81% of the variance of the disease could be attributed to additive genetic factors [3]. In a recent review, multiple environmental factors were suggested to contribute to the evolution of acne. These included high dietary consumption of fatty and sugary foods and dairy products, cigarette smoking, excessive exposure to visible light emitted by cell phones and tablets, improper use of cosmetics, poor sleep quality, psychological stress, elevated environmental temperature, air pollution, excess sun exposure, and use of mineral oils and halogenated hydrocarbons [4]. In many metabolic, autoimmune, and chronic inflammatory disorders, the composition and diversity of the microbiome/dysbiome may notably influence their development [5, 6]. Acne is not an exception. In fact, excessive growth of the bacterium Cutibacterium acnes is evident in acne skin [7]. Therapeutically, multiple treatments are available. Topical skin preparations such as azelaic acid, benzoyl peroxide, dapsone and salicylic acid, antibiotics and retinoids, birth control pills, probiotics, lifestyle changes, and diets low in glycemic index or load have been employed [8].

Pathogenesis of Acne

Acne is usually associated with an excess production of sebum, a fatty material produced by sebocytes in skin pores. This excess causes clogging of pores, which provides an attractive environment for colonization by *Propioni* bacterium acnes and other bacterial species. The resulting infection attracts and activates leukocytes, leading to inflammation within the clogged pores.

Acne is a common complication of polycystic ovary disorder (PCOS), which is characterized by insulin resistance syndrome and excess androgen production [9]. The hyperinsulinemia associated with PCOS acts on ovarian thecal cells to boost their production of the androgen androstenedione, while concurrently suppressing hepatic production of sex hormone binding globulin; the combination of these effects notably enhances free androgen levels [10, 11]. Androgens induce the increased differentiation of sebocytes, and hence increase sebum production [12]. By contrast, the chief current therapy for acne, isotretinoin, induces apoptosis of sebocytes; this pro-apoptotic effect may also underlie this drug's multiple potential side effects [13].

SUPPRESSING LIPOGENESIS AND INFLAMMATION: A ROLE FOR NUTRACEUTICALS

One logical way to attack acne is to suppress lipid synthesis (*de novo* lipogenesis (DNL)) in sebocytes. The transcription factor chiefly responsible for driving this is SREBP-1c [14, 15]. The transcription of the gene coding for SREBP-1c is importantly promoted by the LXR transcription factor [16]. For reasons not fully understood, AMPK activation decreases LXR expression at the

transcriptional level [17]. Also, via inhibition of mTORC1, AMPK impedes the ability of growth factors such as insulin or IGF-1 to promote the proteolytic activation of mature SREBP-1c and also enhance its half-life; these latter two effects are mediated by mTORC1's downstream target p70 S6 kinase [18, 19]. Moreover, AMPK activity opposes DNL by phosphorylating and inhibiting ACC1, an essential initial step in fatty acid synthesis [20]. And systemic activation of AMPK is useful for treating PCOS, by inhibiting gluconeogenesis, while concurrently aiding peripheral glucose uptake, it diminishes insulin secretion, thereby reducing excessive androgen production [21]. Hence, activation of AMPK with a nutraceutical such as berberine could be expected to be useful in both PCOS and acne, as has been suggested by some clinical reports; a typical clinical dose is 500 mg twice daily [22–24].

Sirt1 activity promotes AMPK activation by boosting the expression of LKB1, an enzyme which, in the context of AMP elevation, phosphorylates and activates AMPK [25, 26]. Sirt1 also opposes DNL by deacetylating SREBP1c, thereby reducing its transcriptional activity [27]. *In vitro*, the Sirt1 activator resveratrol has been shown to suppress DNL in sebocytes, an effect abolished by inhibition of either Sirt1 or AMPK [28]. Although the poor human pharmacokinetics of oral resveratrol limit its clinical utility, a number of other nutraceuticals have potential for Sirt1 activation, including ferulic acid, nicotinamide riboside, N1-methylnicotinamide, melatonin, thymoquinone, and the curcumin metabolite tetrahydrocurcumin [29–48]. These options for nutraceutical activation of Sirt1 have been discussed in a recent review [49].

With respect to the inflammation in clogged infected pores, Sirt1 activation would be expected to down-regulate this via deacetylation of the p65 component of NF-kappaB, an effect which inhibits NF-kappaB's transactivational activity [50]. Additionally, it seems likely that comprehensive antioxidant supplementation would be worthwhile, as hydrogen peroxide acts in complementary ways to up-regulate NF-kappaB and MAP kinase activities that drive production of pro-inflammatory cytokines and also mediate their activities [51–53]. Hence, spirulina (whose chromophore phycocyanobilin can mimic free bilirubin's ability to inhibit certain isoforms of NADPH oxidase), a Nrf2 inducer such as lipoic aid, and N-acetylcysteine would likely be useful [54–56]. Although there appears to have been no formal assessments of spirulina or lipoic acid ingestion in acne, topical application of N-acetylcysteine supplementation has been found to be helpful [57, 58]. Plasma levels of eicosapentaenoic acid are reported to be low in acne patients, and supplementation with long-chain omega-3 fatty acids (2 g daily) has shown anti-inflammatory utility in acne - consistent with a role for prostanoids in the inflammation associated with acne [59, 60].

In brief, a rational plan for nutraceutical management of acne could incorporate berberine and one or more Sirt1 activators, complemented by comprehensive supplementation with antioxidants and fish oil.

DIETARY MODULATION OF ACNE RISK

With respect to the impact of dietary choices on acne control, it is notable that plasma free IGF-1, via stimulation of the PI3K-Akt pathway in sebocytes, promotes DNL in these cells by up-regulating SREBP-1c expression and function [61–63]. This results, not only from the mTORC1-p70 S6 kinase signaling discussed above, but also because Akt activation promotes nuclear exclusion of the FOXO1 transcription factor which, within the nucleus, opposes LXR-mediated transcription of the SREBP-1c gene [64, 65]. As one might expect, risk for and severity of acne has been reported to correlate with plasma IGF-1 [66, 67].

Plant-based diets of modest protein content tend to decrease hepatic synthesis and secretion of IGF-1, likely because such diets promote increased hepatic secretion of fibroblast growth factor-21 (FGF-21), which acts in an autocrine manner on hepatocytes to down-regulate their sensitivity to growth hormone [68–70]. Moreover, long-term consumption of such diets tends to have a favorable effect on body fat mass and systemic insulin sensitivity, such that fasting and post-prandial insulin levels are

moderated, an effect likely to decrease ovarian androgen over-production in the context of PCOS [71]. Hence, vegan diets, especially if they feature lower-glycemic-index carbohydrate sources, may be expected to aid acne control [72]. Alternatively, within the context of omnivore diets, the lower post-prandial insulin excursion following meals of low glycemic load tends to decrease free plasma levels of IGF-1 and androgens by up-regulating hepatic production of IGF binding protein-1 and sex hormone-binding globulin [73]. Clinically, low glycemic load diets have been reported to aid acne control [73, 74]. Hence, diets of either high or low protein content appear to have potential in acne prevention and treatment. In this regard, risk for acne appears to be substantially lower in Third World populations consuming their traditional diets that are either plant-based (low protein) or hunter-gatherer (high protein) [75]. This has led to the classification of acne as a "disease of civilization" [76]. In regard to protein, however, high intakes of dairy protein have been associated with increased acne risk, likely because such protein is notably insulinotropic [72, 77].

Figure 1 summarizes the molecular biology underlying DNL and depicts mechanisms whereby certain nutraceuticals or dietary patterns might be expected to quell sebum over-production. Based on clinical applications of nutraceuticals, Table 1 suggests some daily dose ranges for these nutraceuticals that might be expected to have some physiological activity in acne prevention and therapy.

FIGURE LEGENDS

Upregulation of AMPK and Sirt1, and downregulation of IGF-1, propagates downstream pathways that lead to DNL suppression through direct inhibition of ACC1 and deacetylation of SREBP-1c, and by indirect suppression of SREBP-1c transcription. (A) Low-Protein Plant-based diets tend to decrease hepatic synthesis and secretion of IGF-1. (B) Low-glycemic-load Paleolithic diets retain lower levels of insulin which leads to down-regulation of IGF-1 binding protein (IGFBP-1). (C) Berberine and hydrogen sulfide (H2S) have an activation effect over AMPK. (D) Ferulic acid (Ferulate), Nicotinamide riboside (NR), and Melatonin (MT) boost the activities of Sirt1, while AMPK and Sirt1 have an enhancement effect on each other.

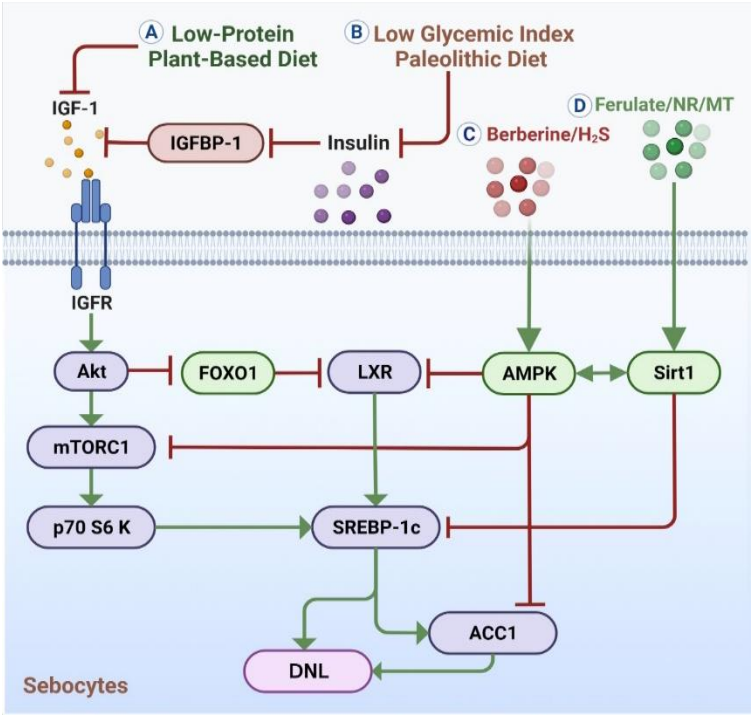

Figure 1. A schematic presentation of nutraceutical and dietary modulation and its effect on *de novo* lipogenesis (DNL) in sebocytes.

Table 1. Nutraceuticals with Potential for Acne Control: Suggested Daily Regimens.

Anti-acne Nutraceuticals	Suggested Dose Ranges
Ferulic Acid	250–500 mg twice daily
Melatonin	5–10 mg at bedtime
Nicotinamide Riboside	300 mg twice daily
Berberine	500 mg twice daily
Spirulina	5–15 g daily
Lipoic Acid	600 mg twice daily
N-Acetylcysteine	600 mg twice daily
Fish Oil Omega-3 Concentrate	1–2 g daily

CONCLUSION

Increased sebum production, reflecting up-regulated DNL in sebocytes, is a key predisposing factor in acne. An analysis of the molecular biology underlying DNL in sebocytes enables the deduction that nutraceuticals boosting the activities of Sirt1 and of AMPK could be expected to diminish the activity of SREBP-1c, master regulatory of DNL. Ferulic acid, melatonin, nicotinamide riboside, and N1-methylnicotinamide have clinical potential for Sirt1 activation, while berberine is a well-documented clinical activator of AMPK. With respect to the inflammation that complicates bacterial infection of clogged pores, Sirt1 activators as well as antioxidants which quell the production or accelerate the catabolism of hydrogen peroxide, e.g., spirulina, lipoic acid, N-acetylcysteine, might be expected to be of some benefit, as might supplementary or dietary intake of EPA-rich fish oil. Diets which lower circulating levels of free IGF-1 and/or insulin likely would decrease sebocyte SREBP-1c activity and DNL by diminishing Akt activation, and those which minimize fasting and post-prandial insulin levels in the context of PCOS should ameliorate androgen over-production. Plant-based diets relatively low in protein and high-glycemic-index carbohydrates, as well as low-glycemic-load "Paleolithic" diets that are high in protein, dietary patterns traditional in many Third World cultures, may therefore be useful for prevention and control of acne. However, it should be stressed that large placebo-controlled randomized cohort studies on the subject are lacking and the concomitantly lipogenic and inflammatory damage is still waiting to prove the present therapeutical strategy.

Abbreviations

De novo lipogenesis: DNL,
Steroid response element-binding protein 1-c: SREBP-1c,
Insulin-like growth factor-I: IGF-1,
Sirtuin 1: Sirt1,
Polycystic ovary disorder: PCOS,
fibroblast growth factor-21: FGF-21,
Adenosine 5′-monophosphate-activated protein kinase: AMPK.

Author Contributions

MFM screened the literature, designed and wrote the manuscript. CB screened the literature, edited and revised the manuscript, designed the figure with BioRender.com permission. AL screened the literature, designed and wrote the manuscript. The three authors agreed to the published version of the manuscript.

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