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Nutritional strategies for psoriasis: current scientific evidence in clinical trials

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Abstract. – OBJECTIVE: Several nutritional strategies for the management of psoriasis are promising. Even if recent data support that nutrition may play a pivotal role in prevention and co-treatment and despite patient's concerns regarding the best nutritional habits, the consensus regarding the nutritional strategies to be adopted lacks in clinical settings. In this manuscript, the effects of several nutritional strategies for psoriasis patients such as hypocaloric diet, vitamin D, fish oil, selenium, and zinc supplementation were systematically reviewed. Randomized controlled trials (RCTs) on beneficial botanical oral supplements were also included in the analysis.

MATERIALS AND METHODS: For each topic, a search was conducted in MEDLINE electronic databases for articles published in English between January 1, 1990 and September 2018. Two independent reviewers assessed and extracted the data. Only controlled clinical trials were selected.

RESULTS: The evidence regarding the current nutritional strategies for psoriasis patients were summarized and translated into a global, comprehensible recommendation.

CONCLUSIONS: Weight loss combined with a healthy lifestyle was shown to be very beneficial for patients with moderate to severe disease with a significant reduction of the Psoriasis Area and Severity Index (PASI) score. Currently, oral vitamin D supplementation for prevention or treatment of psoriasis in adults with normal vitamin D levels is not recommended; however, psoriasis patients with a deficit in plasma vitamin D levels are advised to complement with oral supplements to prevent psoriasis-related comorbidities. Instead of zinc, selenium, and omega 3 supplements have been proven beneficial for psoriasis patients. Among botanical species, *Dunaliella bardawil (D. bardawil), Tripterygium wilfordii (T. wilfordii), Azadirachta indica (A. indica), Curcuma longa (C. longa)*, and HESA-A are the most beneficial. In conclusion, a close cooperation between nutritionists and dermatologists may be useful for the management of psoriasis.

Key Words
Psoriasis, Nutrition, Vitamin D, Obesity, Omega-3, Selenium, Zinc, Botanicals.

Introduction

Psoriasis is an inflammatory, chronic skin disease that significantly affects the patient's quality of life. Psoriasis is a T-cell-mediated autoimmune dermatological disorder and has to be considered a multifactorial disabling condition caused by the interaction between genetic and environmental triggers. Psoriasis affects 0.09-11.43% of the population worldwide, according to the WHO Global Report on Psoriasis[1]. The incidence of psoriasis differs based on geography and ethnicity; a higher prevalence is observed in Caucasians than in Asians and African Americans; in EU, Nordic populations are more affected than Mediterranean. The skin inflammatory process follows a relapsing and remitting course. The pathology may occur at any age, including childhood; however, a peak in psoriasis development occurs at two age ranges (16-22 and 57-60 years)[2,3]. Males and females are equally affected[4]. A mild form of the disease with less than 3% of the skin surface impacted affects two-thirds of patients. The quality of life can be decreased due to psoriasis causing reduced work productivity, increased physical disability, and impaired social relations[5]. Psoriasis is a multifactorial disease caused by the interaction between genetic and environmental triggers[6]. Recently, due to genome-wide association studies, more than 60 disease susceptibility regions related to Th17 cell activation have been identified[6]. Both adaptive and innate immune systems are thought to be responsible for psoriasis pathogenesis. Environmental factors such as emotional stress and smoking can negatively influence the onset of symptoms and the severity of the dis-

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ease[7]. An environmental factor of high interest to patients is the influence of diet[8]; improper nutrition, inadequate body weight, and metabolic diseases may increase the clinical symptoms or even trigger the disease. The immunological response is primarily driven by activated T helper 1 cells, and the consequent release of cytokines results in proliferation of keratinocytes. Interleukins such as IL1β, IL17, IL22 IL23, and TNF-α are involved[9] in the immunological response. During inflammation, regulatory T (Treg) cells play an important role, due to their ability to inhibit the immunological response and maintain the cutaneous immune homeostasis[10] (Figure 1). Studies on animal models of autoimmunity have demonstrated that defects in Treg cell number or function can contribute to autoimmune diseases. This knowledge is now being applied to human autoimmune diseases such as psoriasis. In psoriatic lesions, the epidermal keratinocytes are identified by abnormal proliferation, incomplete differentiation, and decreased apoptosis. Consequently, inflammatory cellular infiltrate is found in both dermis and epidermis[11], and the epidermal barrier at the skin lesion sites is impaired. These lesions induce the typical erythro-squamous psoriatic skin damages, which are preferentially identified on the scalp, elbows, knees, and lower back[12]. Clinical features, especially size and distribution of the psoriatic lesions, allow classification of psoriasis into plaque, guttate, pustular, and erythrodermic types[13]. Currently, the Psoriasis Area and Severity Index (PASI) score is the preferred method to estimate the disease severity and its extent[14]. Skin is the target organ in which psoriasis appears, even if inflammatory responses occur in other areas[13]; evidence indicates that psoriasis is a systemic inflammatory process with comorbidities such as metabolic syndrome[15], adult cardiac disease[16] (CVD), type 2 diabetes mellitus, hypertension, hepatic steatosis (HS), depression[17], and inflammatory bowel disease[18]. These conditions and their related comorbidities can cause relevant physical and psychological burdens in patients affected; thus, several authors consider psoriasis a systemic pathology. Psoriasis and type 2 diabetes share several genetic and immunological abnormalities. It has been reported[19,20] a positive correlation between the severity of psoriasis and the risk of developing diabetes. Glycemic control and its regular monitoring can help to otpimize the quality of life in psoriatic patients and education and diabetes prevention efforts are indicated for psoriasis patients. All strategies, with the inclusion of

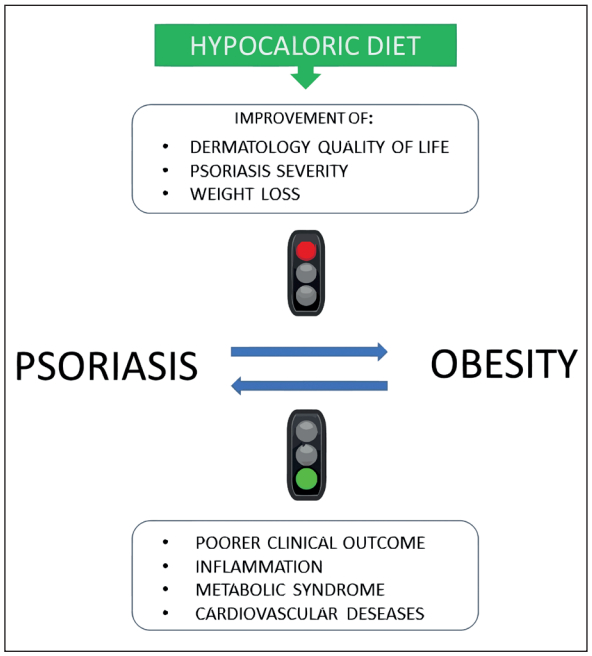

Figure 1. Bidirectional link between psoriasis and obesity and the effect of hypocaloric diet.

nutritional strategies that can successfully prevent future major comorbidities are urgently needed. Recently, it has been reported that keratinocytes of psoriasis patients have a faster turnover compared to normal skin cells and differential glucose requirement. In particular, in skin keratinocytes, Glut1 facilitative glucose transporter is selectively required for keratinocytes proliferation induced by injury and/or inflammation. Indeed, in mouse models of psoriasis-like disease Glut1 inactivation decreased hyperplasia. This scientific evidence suggests that a new therapeutic target can be searched in Glut1 inhibition treatment but further studies need to elucidate the involved mechanisms[21]. To better understand the pathogenesis of psoriasis, Koebner phenomenon was initially reported as the formation of psoriasiform lesions after cutaneous trauma in the uninvolved skin of psoriasis patients[22]. Subsequently, the definition has been extended to lesions developed after trauma in people with no pre-existing dermatosis[23]. Koebner phenomenon is estimated to occur in approximately 25% of psoriasis patients after various traumatic injuries; however, these episodes may be unrecognized. Among the "skin stressor causal factor", there is also tattoos and the number of people that develop this disease after a tattoo is increasing. The introduction of pigments into the skin disturbs the epidermal balance and initiates

a local inflammatory reaction, which may be the first step towards the development of psoriasis in subjects who have never experienced symptoms previously. In these cases, the tattoo can become the triggering element *via* skin inflammation, causing activation of the autoimmune system and leading to the disease[23].

Obesity and Psoriatic Condition

The bidirectional link between obesity and psoriasis is well established with obesity predisposing to psoriasis and psoriasis favouring obesity[24,25] (Figure 2). In a systematic review based on nine studies (a sample size of 134,823 psoriasis patients), Fleming et al[26] suggested that psoriasis patients are more likely to be overweight or obese and a statistically significant association exists between increased psoriasis severity and higher body mass index (BMI). In a systematic review and meta-analysis study published by Upala et al[24] in 2015 that included 7 randomised controlled trials (RCTs; 878 participants) a greater reduction in the severity of psoriasis score (measured with PASI) was observed in patients achieving weight loss reduction due to non-pharmacological interventions compared with controls. Every increase in BMI results in a 9% higher risk of psoriasis onset and a 7% higher risk of increased PASI score[27] (Figure 2). Obese patients have a two-fold increased risk of psoriasis and in epidemiological studies, obesity was shown to lead to a poorer clinical outcome for psoriasis patients[28]. Behavioural actions may play an important role in the correlation between obesity and psoriasis. In fact, a sedentary lifestyle is closely related to psoriasis[29]; psoriasis patients avoid physical activities because the skin pathology may be evident to other people. Obesity, in particular abdominal obesity, is considered a chronic low-grade inflammatory condition where adipocytes secrete proinflammatory signals such as adipokines and cytokines (e.g., TNFα and IL-6)[30,31]. Adipose tissue inflammation is induced by macrophages, resident immune cells that constitute the second largest cellular component after adipocytes in adipose tissue. Obesity causes changes in the number and functional activity of macrophages resulting in the activation of local and later systemic inflammatory responses, triggering the transition from simple adiposity to diseases such as type 2 diabetes, ischemic heart disease, and arterial hypertension. The overall prevalence of pediatric psoriasis is estimated at approximately 2%, with 20,000 children younger than 10 years of age diagnosed yearly[32]. In an international cross-sectional study[15], the odds ratio (OD) of obesity (BMI ≥ 85th percentile) in children with psoriasis was 3.60 and 4.92 for

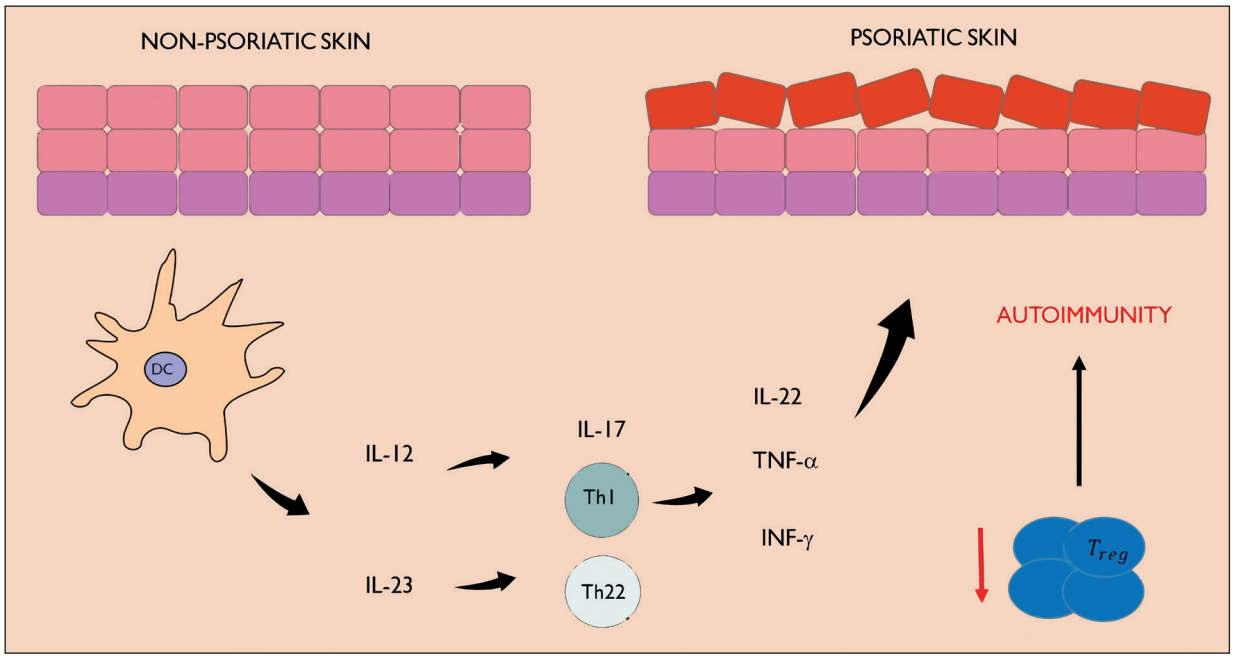

Figure 2. Immunological response in non-psoriatic skin and in psroatic skin. IL = interleukin, TNF-α = tumor necrosis factor-alpha, IFN-γ = interferon-gamma; Treg = regulatory T cells; DC = dendritic cells.

mild and severe disease, respectively, compared with controls. Similar findings were observed in a case-control study of children 5-15 years of age with moderate to severe plaque psoriasis, where the odds of having a BMI $\geq 85^{th}$ percentile for psoriatic children was more than 4-fold compared with controls[33] (OR = 4.4). In a prospective trial[34] comparing 20 children 9-17 years of age with psoriasis ($\geq$ 5% of body surface area) or psoriatic arthritis, 30% of children met the criteria for metabolic syndrome, compared with 5% in the control group. Psoriasis is associated with metabolic syndrome[35] and a higher cardiovascular risk[36]. In a cross-sectional study[37], psoriasis was shown to be associated with metabolic syndrome and worsen with increasing disease severity. These findings were later substantiated in a 2013 meta-analysis[38], where the pooled OR for metabolic syndrome was 2.26. These data indicate that clinically, psoriasis patients should be considered as a pivotal step for patient assessment. Current clinical data[39,40] show that nutritional consultation may help psoriasis patients in either the treatment of the disease severity or decrease the obesity-related comorbidities.

Hypocaloric Diet as a Nutritional Strategy for Psoriasis

As previously shown, a well-established bidirectional link exists between psoriasis and obesity. Obesity is associated with increased psoriasis incidence, higher psoriasis severity, and reduced response to conventional psoriasis treatment. Weight reduction, as a result of intervention with a tailored hypocaloric diet, it can be helpful to patients with psoriasis who are overweight or obese, leading to significant improvement in psoriasis severity[41-44]. An investigator-blinded clinical RCT was conducted with 61 patients. Diet and subsequent body weight reduction increased the therapeutic response to cyclosporine in obese patients with moderate-to-severe chronic plaque psoriasis[41]. Compared with controls, the patients in the hypocaloric diet group had significantly greater improvement in psoriasis severity. The same result was obtained in a prospective RCT testing the effects of a 24-week low-calorie diet ($\leq$1000 kcal/day) on 262 overweight/obese psoriasis patients receiving biologic therapy. Compared with the controls, patients in the hypocaloric diet group had a significantly greater reduction in psoriasis severity and body weight[42]. Guida et al[43] conducted a prospective study on the effects of a 6-month hypocaloric diet in 44 obese patients and observed decreased psoriasis severity, dermatologically better quality of life, and lower body weight compared with controls. The effects of dietary intervention combined with physical exercise on weight loss were investigated in 303 overweight or obese patients with moderate-to-severe chronic plaque psoriasis. Patients included in the study did not achieve remission after 4 weeks of continuous systemic treatment. The patients were divided into two groups: one group followed a 20-week dietary plan associated with physical exercise for weight loss and another group received only simple informative counselling regarding the benefits of weight loss for psoriatic disease. Sessions of physical exercise included aerobic physical exercise for at least 40 minutes 3 times a week. PASI score reduction was statistically significantly different in approximately 48% of subjects in the dietary intervention group compared with 25% of subjects in the information-only group. In conclusion, 20 weeks of dietetic intervention with increased physical exercise reduced psoriasis severity in overweight or obese psoriasis patients[44]. In a prospective study by Jensen et al[45] patients with obesity and psoriasis were observed for 16 weeks, a significant improvement in psoriasis severity, dermatologically better quality of life, greater weight loss, and clinically improved important PASI scores in patients who received a hypocaloric diet compared with controls. The intervention group received a low-calorie diet (800-1,000 kcal/day) for 8 weeks followed by 8 weeks of reintroduction (1,200 kcal/day). The beneficial effects of weight reduction on the severity of psoriasis and amounts of plasma glucose and glycated haemoglobin were maintained at 1 year[45]. In a clinical RCT[46], 42 obese patients after discontinuing methotrexate therapy, began a hypocaloric diet regimen or a free diet for 24 weeks and were followed-up for an additional 12 weeks. Maintenance of psoriasis remission was not significantly different between patients following a hypocaloric or free diet, and relapse was already observed at week 12; however, the remission tended to be better in the intervention group. In another study[47], 138 overweight/obese patients with psoriatic arthritis starting treatment with TNF-α blockers were divided into two groups: 69 patients received a hypocaloric diet and 69 a freely managed diet. TNF-α may contribute to the extent of psoriatic lesions in obese patients. Blocking TNF-α production helps interrupt the inflammatory cycle of psoriatic disease, but does not improve insulin sensitivity in obese patients

with type 2 diabetes[47]. Changes in metabolic variables were measured, and a complete clinical rheumatologic evaluation was performed in all patients at baseline and after a 6-month follow-up to determine whether Minimal Disease Activity (MDA) criteria was achieved. Regardless of the type of diet, a successful weight loss of more ≥5% from baseline values during treatment with TNF-α blockers was associated with a higher rate of MDA criteria achieved in overweight/obese patients with psoriatic arthritis[47]. Bariatric surgery may be considered an extreme approach for the treatment of psoriasis; however, for obese patients with many comorbidities, the Roux-en-Y gastric bypass has been the most effective[48,49]. Romero-Talamás et al[50] reported that among 33 highly obese patients under active medical treatment for psoriasis and subjected to a bariatric surgery, nearly 40% experienced a relevant improvement in clinical severity of psoriasis positively associated with the rate of postoperative weight loss. No RCT studies are available in which the effect of a low-calorie diet or weight reduction surgery in children was evaluated. A recent review[51] showed that hypocaloric diet improves weight and dermatological state as an adjuvant intervention to standard medical treatments such as cyclosporine, methotrexate, biologic therapy, and phototherapy. Diet alone may not be sufficient to maintain a low psoriatic score achieved by therapeutic remission in patients that discontinue their medical treatment[17,46]. Education regarding diet, nutrition, weight, and physical activity are important in the prevention and treatment of psoriasis and should be a first line intervention aimed at improving patient prognosis[52].

Mediterranean Diet (MD) and Psoriatic Condition: What is Known

The Mediterranean Diet (MD) distinguishes itself amongst others by a prevalent intake of fruit, green and yellow vegetables, whole cereals, potatoes, beans, nuts, seeds and other kinds of food, which are very rich in antioxidants and polyphenols. The source of fats is represented by Extra Virgin Olive Oil (EVOO), whereas animal fats such as butter, cream, and lard are not included. Dairy products (mainly light cheese and yogurt), fish and poultry are consumed in low-to-moderate percentages whereas wine, red meat, and eggs are limited. Many epidemiological studies have suggested that the MD offers beneficial health effects, especially upon cardiovascular, metabolic, neoplastic and chronic inflammatory diseases. Recent data provided by Barrea et al[53,54] demonstrates that there is a significant correlation between adherence to the MD, assessed using the PREDIMED trial[55], and the PASI score which describes the severity of psoriasis. In particular, the results showed that the less the MD was adhered to, the higher the percentage of psoriatic patients was if compared to the control group. PREDIMED questionnaire shows that EVOO and fish consumption have an autonomous predictive rate for PASI score and C-reactive protein (CRP) levels, which is the main protein of the acute phase of inflammation. Psoriatic patients evidenced a statistically significant decrease in the use of MD dietary components (EVOO, fruits, fish, and nuts) and a statistically significant increase in the use of red processed meats compared to healthy controls. Furthermore, a higher consumption of EVOO is associated to a lower psoriasis severity, supporting, even more, the possible positive effects of MD in psoriasis patients[53]. In addition, Barrea et al[54] have proved that psoriatic patients have a higher intake of simple carbohydrates, total fat and ω-6/ω-3 PUFA ratio together with a lower consumption of proteins, complex carbohydrates, MUFA, ω-3 PUFA, and fibers. The PUFA metabolism is most active in the skin. Therefore, essential fatty acid (EFA) cutaneous deficiency can be related to epidermal hyperproliferation and increased the permeability of the epidermal barrier. Linoleic acid (LA) is an epidermal component of ceramides, which are useful to avoid epidermal water loss and to maintain its permeability. LA dietary deficiency may consequently cause scaly disorder. High levels of arachidonic acid and of its derivatives with pro-inflammatory activity are present in cutaneous lesions of psoriatic patients. The following two conditions can occur simultaneously, contributing to disease:

- High levels of arachidonic acid due to the action of phospholipase A2 on phospholipids of the cellular membrane;
- Low Omega 3/Omega 6 ratio due to dietary deficiency[56,57].

An anti-inflammatory condition is therefore achievable by a reduction of arachidonic acid and an incremental intake of eicosapentaenoic acid (EPA)[58].

A tailored MD with high intake of MUFA and ω-3 PUFA, vegetables, fruit, and fibers, together with a restricted intake of saturated fats, simple carbohydrates, and sugars, should be suggested as a nutritional approach in psoriatic patients.

Vitamin D and Psoriasis

Although topical treatment with vitamin D is well established and represents an effective and safe treatment option in combination with topical corticosteroids[59,60], the beneficial effects of vitamin D oral supplementation remain uncertain. Mammals acquire vitamin D in two ways, *via* synthesis in the skin by the sun (or other UVB sources) or from the diet. The biologically active form of vitamin D is 1,25-dihydroxyvitamin D3. The main source of vitamin D3 is also from exposure to sunlight, accounting for more than 90% of the body's vitamin D requirement. The active form of vitamin D and its receptor regulates the differentiation and proliferation of keratinocytes, the balance of the cutaneous immune system, and the process of apoptosis. Recent data[69] have shown that serum vitamin D levels are lower in psoriasis patients. Furthermore, an inverse correlation between low vitamin D status and psoriasis has consistently shown a deficiency of serum concentration of 25-hydroxyvitamin D correlates with severity of disease in chronic plaque psoriasis[62]. Hypothetically, low vitamin D status is associated with obesity and psoriasis. Based on this hypothesis, vitamin D supplementation might aid in the prevention of psoriasis-related comorbidities. A study by Merola et al[63] on 70,437 female nurses in the United States using self-administrated semi-quantitative food frequency questionnaires in 1994, 1998, 2002, and 2006 showed that vitamin D intake had no impact on the development of psoriasis.

Vitamin D might represent a key modulator of immune and inflammatory mechanisms[64]. The immune regulatory properties of vitamin D are mediated, at least partially, through regulatory T cells (Treg) induction. Following presentation by tolerogenic dendritic cells, Treg can be induced in the peripheral tissues from naive cells[64]. An interruption of the immunological homeostasis and a reduction of the inflammation process in psoriasis patients might be due to low vitamin D levels which decrease the number of circulatory Treg[64]. To analyze the impact of vitamin D on psoriasis patients, electronic databases in MEDLINE were searched for clinical trials published up to 1990. The systematic search strategy using the combined terms "psoriasis" and "Vitamin D" identified 1,510 papers. After full-text screening and eligibility criteria analysis, four papers were finally selected and are reported in Table I[65-68]. Only RCTs were selected. In all studies, the effects of oral supplementation with 1,25-dihydroxyvitamin D3 for 3-12 months was reported. Sample size varied from 19-101 psoriasis patients. In 3 of the 4 studies, no statistically significant effect of vitamin D supplementation on psoriasis severity was reported[65,68,69]; however, a correlation between serum vitamin D level and psoriasis severity was observed in one study[69]. An improvement of immunological parameters was reported by Gaal et al[66] in patients with psoriatic arthropathy. In conclusion, oral vitamin D supplementation for prevention or treatment of psoriasis in adults with normal vitamin D levels is currently not recommended[51]. However, individuals deficient in plasma vitamin D should complement with oral supplements to prevent psoriasis-related comorbidities.

Reference for the right assessment of vitamin D intake can be found in Dietary Reference Values (DRVs) for nutrients Summary Report recently approved by European Food and Safety Authority (EFSA) panel on Dietetic Product 2017. Concerning vitamin D, EFSA defined the adequate intake (AI) in adults, pregnant, breastfeeding women, children (> 12 months), and teenager equivalent to 15 µg/day under conditions of assumed minimal cutaneous vitamin D synthesis.

This AI level should guarantee a normal plasma level in healthy subjects and should not believe as therapeutic level for psoriatic treatment: improving psoriasis has not to be considered as an outcome in DRVs-EFSA evaluation.

Psoriasis and Microbiota

Recent evidence has highlighted the pivotal role of microbiota in the pathophysiology of chronic inflammatory diseases and of its impact on the efficacy of therapeutic agents. Besides local symbiotic interactions between gut and microbiota, more complex systemic effects, including the skin, act on the rest of the body[70]. The dominant types of bacteria in healthy skin assure a stable microbiota. This is constituted by four bacterial phyla: *Actinobacteria, Firmicutes, Proteobacteria,* and *Bacteroidetes*. Among *Bacteroidetes,* the genera *Corynebacterium, Propionibacterium,* and *Staphylococcus* are the most abundant[71-73]. Host-dependent factors such as lifestyle, medical treatment, immune system, and external environment, have a direct influence on the composition of skin microbiota[71]. Skin microbiota composition is related to different dermatological diseases including psoriasis, atopic dermatitis, and acne vulgaris[74,75]. Microbiota colonizing psoriatic plaques have been investigated, and a decreased relative abundance of *Propionibacterium* was described[70,76,77]. In a larger study that enrolled 75

Table I. Selected studies regarding the effects of vitamin D supplementation in psoriasis patients. RCT: randomized clinical trial; DBPCT: double blind placebo controlled trials. Tools used to measure the severity and the extent of psoriasis: Psoriasis Area Severity Index (PASI), Physicians Global Assessment (PGA), Dermatology Life Quality Index (DLQI), and Psoriasis Disability Index (PDI).

Author	Number of patients (dropout excluded)	Study design	Supplement 1αoh Vitamin D3	Supplementation duration (months)	Study endpoints	Conclusions
Siddiqui et al[65]	50	DBPCT	1 μg/day	3	PASI	No significant difference between treated and placebo group.in moderate to severe psoriasis
Gaal et al[66]	19	RCT	0.5 μg/day	3	Immunomodulatory effect	Significant immunomodulatory effect in patients with polyarticular psoriasis.
Jarrett et al[67]	65	RPCT	100,000 IU monthly	6	PASI, PGA, DLQI, PDI	No significant difference between treated and placebo group
Ingram et al[68]	101	RPCT	100,000 IU monthly	12	PASI and serum 25(OH)D concentrations assessed at 3-monthly intervals	No direct benefit of vitamin D3 supplementation. In some subgroups relationship between 25(OH)D and psoriasis severity

patients with psoriasis (and 124 healthy controls), two distinct clusters, called cutaneotypes, were identified: a *Proteobacteria*-associated microbiota, and a *Firmicutes* and *Actinobacteria*-associated microbiota. This last cutaneotype was enriched in lesion specimens when compared to controls[78] (odds ratio 3.52). The trigger that causes the shift from a host-symbiosis to a host-dysbiosis microbiota interaction in the skin is not yet fully investigated. Longitudinal studies addressed to investigate the dynamics of microbiota composition during plaque resolution, and relapsing could provide new insight into the role of microbiota during triggering, propagation, and maintenance of plaques[79].

The gut and the skin are intricately related through what is referred to as the "gut-skin axis"[80]. In psoriatic patients, gut microbiota seems to be considerably modified, with a significantly reduced abundance of *Akkermansia muciniphilia* when compared to healthy controls[81]. A randomized double-blind placebo-controlled trial[82] evidences that patients treated with a daily oral dose of *Lactobacillus parcasei* NCC2461 exhibit decreased skin sensitivity, have a hastened barrier function recovery and preserve skin more efficiently after treatment with agents such as sodium lactate and urea. Mice fed with *Lactobacillus pentosus* developed a milder form of imiquimod-induced psoriasis when compared to control mice[83] and had lower levels of pro-inflammatory cytokines[84] (TNF-α, IL-6, IL-23, IL-17, IL-17F, and IL-22). The role of *Lactobacillus pentosus* in psoriasis patients still needs to be investigated. The development of microbiota-targeted therapy and its potential use for novel diagnostic approaches to cutaneous diseases is still in progress[75].

Nutritional Supplements Used by Psoriasis Patients Other Than Conventional Medicine

Complementary medicine, which uses unconventional substances/treatments, has always been common among eastern populations and is currently gaining popularity in the western world. According to the National Center for Complementary and Integrative Health (USA), complementary medicine includes a wide range of products such as herbs, medicinal mushrooms, vitamins, minerals and probiotics, and several practices such as magnetotherapy, or acupuncture. When a non-mainstream treatment is used in place of conventional medicine, it is considered 'alternative' (definition of Complementary and Alternative Medicine, CAM, according to the National Center for Complementary and Integrative Health). When a non-mainstream treatment is used together with conventional medicine, it is considered 'complementary' (Complementary

and Integrative Alternative Medicine, CIM). Dermatology has experienced a trend toward CAM; one review evaluating seven dermatological surveys showed a 35-69% of prevalence in CAM use by patients[69]. Because the simultaneous conventional and CAM practices could potentially cause both side effects and benefits, investigating any alternative or integrative therapies used as substitutes or supplemental medicine to the conventional therapy is useful for dermatologists. If self-administered, complementary medicine is to be avoided for any reason, the beneficial effects of macro- and micronutrient supplementation for improving psoriasis condition should be considered. The most common oral dietary supplements used by psoriasis patients are fish oil, selenium, and zinc[85,86]. Fish oil and omega 3 supplements are the most commonly used CAM supplements not only by psoriasis patients[87] but also patients with other dermatological diseases. Millsop et al[40] reviewed the study on the efficacy of fish oil supplementation in psoriasis patients; 12 of 15 trials selected as controlled studies showed a benefit. The dosage varies; however, the average dose of eicosapentaenoic acid (EPA) was 4 g/day and of docosahexaenoic acid (DHA) was 2.6 g/day. These supplements should be taken for longer periods (from 1-6 months) to obtain an effective improvement in psoriasis. In one study, eating just 6 ounces (170 g) of fatty fish daily was shown to improve psoriasis when compared with white fish consumption[40]. Among oral supplements used by psoriasis patients, data regarding oral supplementation with zinc is controversial[88]. Despite the general use of zinc oral supplementation in psoriasis patients, RCTs were conducted in only two old studies. In a double-blind crossover trial by Clemmensen et al[89] with 24 patients suffering from psoriatic arthritis, oral zinc sulphate was found effective without any severe side-effects. Conversely, Burrows et al[90] reported no statistically significant differences in psoriasis and severity index scores associated with zinc sulphate supplementation in 24 chronic psoriasis patients over a 12-week period. Selenium is an essential element with antiproliferative and immune regulatory properties. Decreased serum selenium levels were associated with increased psoriasis severity. A study by Wacewicz et al[91] showed that, when alterations in the serum levels of selenium, zinc, copper, total antioxidants, and C-reactive protein (CRP) occur, supplementation with selenium is advised. In a relevant study[92], psoriasis diseases were treated with an oral combination of coenzyme Q10 (50 mg daily), vitamin E (50 mg daily), and selenium (48 μg daily) with positive effects. Furthermore, in a study[93] consisting of 34 patients, oral supplementation with a combination of micronutrients (folic acid, magnesium, iron, zinc, copper, manganese, selenium, chromium, iodine, and vitamins A, D, E, K, C, B1, B2, B3, B6, and B12) for 3 months in conjunction with low-dose methotrexate significantly improved psoriasis severity. Concomitant treatment with methotrexate and micronutrients in a randomized double-blind trial[94] showed an improvement in PASI score and a significant decrease in IL-1β and TNF-α levels with a significant correlation between changes in both IL-1β and TNF-α levels and PASI score. Due to limited data regarding the effectiveness of selenium supplementation, no recommendation is available to date for the use of selenium as a supplement for the treatment of psoriasis. Based on the extensive use of CAM agents in the treatment of psoriasis, the most common and effective oral botanicals have been recently reviewed[85,95,96]. The green microalga *Dunaliella bardawil* (*D. bardawil;* Ben-Amotz and Avron), is referred as the richest known source of β-carotene. Found in natural salt lakes, salt ponds, and hypersaline coastal pools, *Dunaliella salina* (*D. salina*) is halophilic and distributed worldwide[97]. Apart from beta-carotene, at least nine categories of secondary metabolites from *D. salina* have been reviewed because they show antioxidant, anti-cancerous, anti-inflammatory, eye-sight improving, and antimicrobial properties[98]. Greenberger et al[99] tested the oral assumption of *D. bardawil* in 34, mild, chronic plaque psoriasis patients. Due to the significant increase of all-trans beta-carotene plasma levels, PASI score decreased in 61.3% of patients, almost double than in controls (6 weeks). Although statistical significance was not reached, the Dermatology Life Quality Index (DLQI) confirmed a positive trend at 12 weeks compared with controls (Table II). *Tripterygium wilfordii* Hook F (TwHF; *Celastraceae*) is native to South Central China and is an important herb used in traditional Chinese medicine (TCM) against several autoimmune and inflammatory diseases. TwHF is reported to contain bioactive triptolides and terpenoids[100-102] particularly effective in the treatment of rheumatoid arthritis[103]. Regarding the application of TwHF in the treatment of psoriasis vulgaris, Lv et al[104] reviewed numerous RCTs in the literature focusing on internal use and considering the PASI score as the main outcome. Significant reductions of PASI score at least up to PASI 70

Table II. Selected studies regarding the effects of oral botanicsls for psoriasis. RCT: randomized clinical trial; DBPCT: double blind placebo controlled trials; DB: double blind. Tools used to measure the severity and extent of psoriasis: Psoriasis Area Severity Index (PASI), Physicians Global Assessment (PGA), Dermatology Life Quality Index (DLQI).

Author	Treatment	Number and type of psoriasis	Study design	Dose and duration	Methods	Efficacy	Adverse effects
Greenberger et al[99]	*Dunaniella bardawil*	34, mild, chronic	Prospective, DB	1 capsule/day, 6 weeks	PASI score, DLQI	PASI score improvement in treatment compared to control; not significance in DLQI between two groups	None
LV et al[104]	*Tripterigium wilfordii*	1872	Systematic review, 20 RCT	Tripterygium glycosides 10-30 mg/day, 1-3 months	PASI score	PASI score improvement in treatment compared to control	Several mild side effects
Pandey et al[108]	*Azadirachta indica (neem tree)*	50	RCT	3 capsules/day, 12 weeks	PASI score	PASI score improvement in treatment compared to control	None
Strong et al[115]	*Oenothera biennis*	51	DBPCT	12 × 500 mg capsules combined with fish oil, 7 months		No significant difference was noted in the rate of deterioration	None
Oliwiecki et al[116]	*Oenothera biennis*	37	DB, parallel trial	12 × 500 mg capsules, combined with marine oil, 6 months	Assesment of erythema, scaling and overall severty	No significant improvement in clinical severity of psoriasis or change in transepidermal water loss	None
Antiga et al[119]	*Curcuma longa*	63, mild to moderate	DBPCT	2 g/day combined with topical steroid	PASI score	PASI score improvement in treatment compared to control	One patient had diarrhea
Carrion-Gutierrez et al[120]	*Curcuma longa*	21, moderate to severe	RCT Double blind	6 Tablets x12 mg curcumin/day and visible light phototherapy	PASI score	Therapeutic response present if coupled with visible light phototherapy	None
Kurd et al[121]	*Curcuma longa*	12, moderate to severe	Prospetive, controlled,	4.5g/day, 12 weeks open label	PASI score, PGA	Only two patients achieved PASI 75 or a PGA of excellent	GI upset or heat intolerance/ hot flashes
Ahmadi et al[130]	HESA-A	28, chronic	RCT	2X25mg/Kg tablet for 6 months	Clinical determination of psoriasis severity	64,2% clearance of psoriatic plaques and 35.8% had mild disease	None
Barikbin et al[131]	HESA-A	19, chronic	RCT	30 mg/Kg, 4-30 weeks	PASI score	PASI score reduced in 73,7% and increased in 6.3%. Statistically significant correlation between the duration of treatment and PASI improvement	None

were reported in all the reviewed publications. Based on a meta-analysis of the same literature, Lv et al[104] refuted the previously suggested unfavourable cost-to-benefit ratio of several mild adverse effects[105] from TwHF such as gastrointestinal reactions, skin dryness, and increased urea nitrogen (Table II). *Azadirachta indica* A. Juss (*A. indica; Meliaceae*), the neem tree, is native to regions from Assam to Indochina and has been used for thousands of years in traditional Indian medicine against a plethora of diseases. In numerous studies, bioactive metabolites isolated from *A. indica* and the wide range of their actions have been investigated, even for the treatment of dermatological diseases[106,107]. However, the only evidence for its efficacy in the treatment of psoriasis was reported by Pandey et al[108], where a significant decrease in PASI score was observed after 12 weeks of consuming *A. indica* in a RCT of 50 patients. According to the authors, this may be due to the inhibition of prostaglandin synthetase by nimbidin, a secondary metabolite present in *A. indica* essential oil[109] (Table II). *Oenothera biennis L.,* the evening primrose, is native to Mexico and Eastern USA. The evening primrose seed oil (EPSO) has been reported effective against several diseases including dermatitis and psoriasis, mainly due to its unsaturated fatty acid component and phytosterols[110-114]. In two reports[115,116], a supplement made by a combination of fish oil or marine oil (omega-3 source) and EPSO (omega-6 source) was used. No substantial difference was reported in the treatment of psoriasis when compared with placebo (Table II). *Curcuma longa* L. (*C. longa*), the spice turmeric, is a sterile domesticated plant not found in the wild, and thought to originate in South or Southeast Asia by selective and vegetative propagation of a hybrid between wild turmeric (Curcuma aromatica) and another closely related species (http://www.plantsoftheworldonline.org). This species has been used for millennia in TCM and Ayurveda due to its wide range of medicinal benefits[96,117]. However, the efficacy of curcumin, the main bioactive compound in *C. longa*, has been refuted by Nelson et al[118] on the basis of instability, reactivity, and poor bioavailability, as well as the inadequacy of most trials. In terms of treatment for psoriasis, curcumin has been suggested in published RCTs to have an adjuvant instead of a main role. According to Antiga et al[119], oral curcumin acts as an adjuvant in topical steroid treatment by reducing serum IL-22 levels and leading to lower PASI scores. Carrion-Gutierrez et al[120] showed oral curcumin is a photosensitiser and thus an adjuvant in phototherapy. Conversely, Kurd et al[121] reported a low response rate when oral curcumin was the only supplement administered as treatment (Table II). Patented under Iranian authority, HESA-A is manufactured according to the traditional Persian medicine and composed of mineral, herbal, and animal (marine shrimp) fractions[122-124]. Because HESA-A is mainly a herbal compound, all the components belong to the *Apiaceae* family; *Kelussia odoratissima* (*K. odoratissima*) Mozaff. (wild celery) is coupled with *Cuminum cyminum* (*C. cyminum*) L. (cumin), alternatively, *Apium graveolens* (*A. graveolens*) L. (cultivated celery) is coupled with *Carum carvi* (*C. carvi*) L. (wild cumin). Only *K. odoratissima* is endemic to Iran, whereas the other mentioned species share a wider native range in eastern Asia, Europe, and North Africa. Each species in HESA-A has been reported to have medicinal properties; *K. odoratissima* is effective against food-borne pathogenic bacteria[125]. Antibacterial, antifungal, and anti-inflammatory properties have also been reviewed for *A. graveolens* as well as *C. cyminum* and *C. carvi*[126-128]. Among the numerous effects associated with *C. cyminum*, the reduction of skin disorders has been attributed to the high content of vitamin E, whereas vitamins A and C are higher in *A. graveolens*[129]. HESA-A has been tested in patients with chronic plaque psoriasis. Ahmadi et al[130] reported complete or substantial remission of the plaques after 4-6 months of treatment in all treated subjects. Although Barikbin et al[131] reported contradictory results when the treatment period was reduced to 4 weeks, a significant correlation between duration of the treatment and improved PASI score consistently suggests HESA-A is more suitable for long-term therapy (Table II). Overall, despite the prospective efficacy of several of the above-mentioned CAM agents in the treatment of psoriasis, additional clinical trials are needed in the future to better understand the activity of these agents, considering the increased use of CAM remedies among patients.

Conclusions

The multifactorial causes and the chronic nature of psoriasis require a systematic approach based on an adequate interaction between nutrition and supplementation that might act synergistically to

prevent the onset or reduce psoriasis severity and consequently, improve the quality of life and mitigate the symptomatology of psoriasis diseases. A bidirectional connection exists between psoriasis and obesity. For this reason, weight loss combined with a healthy lifestyle has been proven beneficial for patients with moderate to severe disease to obtain a significant reduction of PASI score. Several questions remain regarding the role of a hypocaloric diet on psoriatic condition:

- Is psoriasis severity reduced by the type of diet and/or the weight reduction?
- What is the amount of weight reduction necessary for clinical efficacy?
- What is the efficacy of different diets and their long-term benefits?
- What is the effect of weight reduction in normal-weight patients?
- What is the role of exercise in conjunction with dietary weight reduction?

Education regarding modifiable environmental factors including diet and nutrition, avoiding excessive alcohol consumption and smoking, as well as promoting physical activity have been recognized as primary interventions for the management of psoriasis.

Particular attention should be paid to the CAM agents, increasingly used among psoriasis patients, to obtain specific guidelines for patients and dermatologists. Oral supplements proven useful in recent studies are fish oil and selenium. The purpose of vitamin D supplementation in hypovitaminosis D patients is to decrease the risk of cardiovascular disease, psoriasis, and associated comorbidities; however, study results regarding oral zinc supplementation are controversial. Several oral botanicals such as *D. bardawil*, TwHF, *A. indica*, *C. longa*, and HESA-A have been reported in RCTs to improve psoriasis severity. Due to the many important factors, the current management of psoriasis patients should be re-evaluated and an integrated multidisciplinary approach, from prevention to comorbidities assessment, considered. Education to modify lifestyle and environmental risk factors is a pivotal step[132]. A collaboration between nutritionists and medical specialists with a holistic approach may be useful for psoriasis patients.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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