Nutritional Interventions In The Treatment Of Acne Vulgaris: A Systematic Review Of Clinical Trials

Intervenções Nutricionais No Tratamento Da Acne Vulgaris: Uma Revisão Sistemática Dos Ensaios Clínicos

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ABSTRACT
The aim of this study is to review the literature about dietary interventions on acne vulgaris in order to support the development of more effective treatments in clinical practice. A systematic review of the literature, from clinical trials over the last five years, available in *Pub Med* and *SciELO*. The selected articles were analyzed according to the Jadad scale, CONSORT and risk of bias using the Cochrane protocol. CONSORT indicated that most of the evidence score was attributed in the titles, abstracts and some of the methods. In particular, the methods of the studies evaluated, when lacking detail, received lower scores, among the evidence, expressed as a percentage. The results, after using the Jadad scale, indicated a similar profile to that obtained with the CONSORT protocol. However, this tool is limited with regard to randomization and blinding. Using the Cochrane method, the risk of bias was evaluated. Results corroborated the evaluations by CONSORT and Jadad scale. Supplementation with n-3 fatty acids, *Camellia sinensis*, *Berberis vulgaris*, chromium, selenium and probiotics were significant, but results were limited for the treatment of acne vulgaris. Consumption of foods with increased glycemic load and chocolate indicated a correlation with an increase in acneiform lesions. Changes in nutritional status of alfa-tocopherol, cobalamin and folic acid were associated with the use of isotretinoin. There is a need to increase the quantity and quality of scientific evidence on the nutritional treatment of acne vulgaris in order to more effectively and safely guide the nutritional actions of clinical practice today.

Keywords: acne vulgaris, nutritional supplementation, bioactive compounds, inflammation, dermatology

ABSTRACT
O objectivo deste estudo é rever a literatura sobre intervenções dietéticas sobre acne vulgaris, a fim de apoiar o desenvolvimento de tratamentos mais eficazes na prática clínica. Uma revisão sistemática da literatura, a partir de ensaios clínicos dos últimos cinco anos, disponível em Pub Med e SciELO. Os artigos seleccionados foram analisados de acordo com a escala Jadad, CONSORT e risco de enviesamento utilizando o protocolo Cochrane. O CONSORT indicou que a maioria da pontuação da prova foi atribuída nos títulos, resumos e alguns dos métodos. Em particular, os métodos dos estudos avaliados, quando faltavam detalhes, receberam pontuações mais baixas, entre as provas, expressas em percentagem. Os resultados, após a utilização da escala Jadad, indicaram um perfil semelhante ao obtido com o protocolo CONSORT. Contudo, esta ferramenta é limitada

no que diz respeito à aleatorização e cegamento. Utilizando o método Cochrane, foi avaliado o risco de enviesamento. Os resultados corroboraram as avaliações por CONSORT e a escala de Jadad. A suplementação com ácidos gordos n-3, Camellia sinensis, Berberis vulgaris, cromo, selénio e probióticos foi significativa, mas os resultados foram limitados para o tratamento da acne vulgaris. O consumo de alimentos com aumento da carga glicémica e chocolate indicou uma correlação com um aumento das lesões acneiformes. Alterações no estado nutricional de alfa-tocoferol, cobalamina e ácido fólico foram associadas à utilização de isotretinoína. Há necessidade de aumentar a quantidade e qualidade das provas científicas sobre o tratamento nutricional da acne vulgaris, a fim de orientar mais eficaz e seguramente as acções nutricionais da prática clínica actual.

Palavras-chave: acne vulgaris, suplemento nutricional, compostos bioactivos, inflamação, dermatologia

1 INTRODUCTION

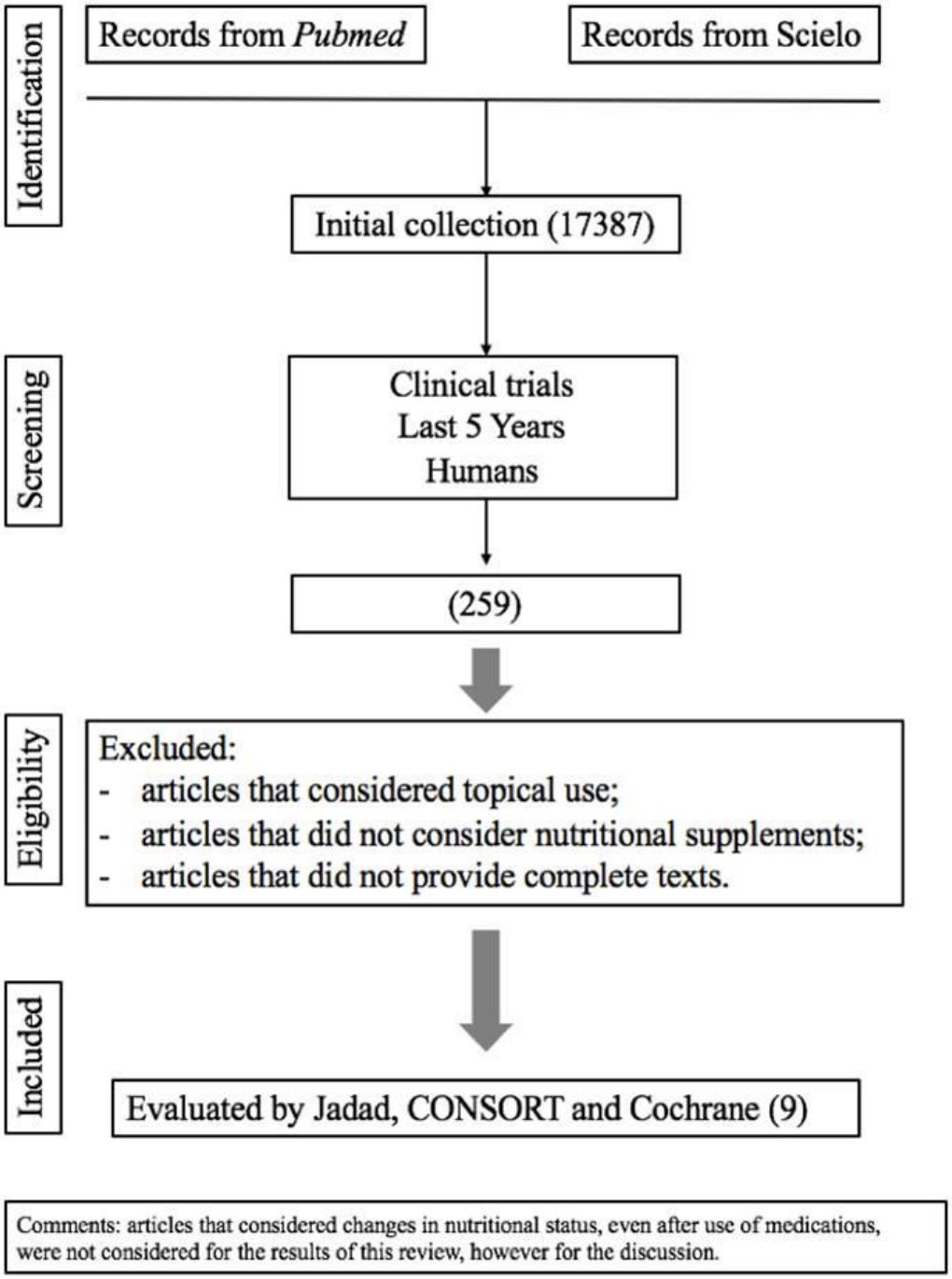
Acne vulgaris is a chronic dermatosis, highly prevalent in the western population, and common among adolescents. It is characterized by follicular keratinization, intense secretion of sebum, colonization of *Propionibacterium acnes*, with intrafollicular overgrowth and inflammation. There are different stages of lesions: open and closed comedones (noninflammatory lesions), papules and pustules (inflammatory lesions). This acne, then, which is usually approached as an aesthetic problem, can have repercussions for a lifetime, such as low self-esteem, with emotional and social consequences, which may compromise quality of life[1,2,3,4]. It is estimated that approximately 9.4% of the world population has acne vulgaris, ranking it as the eighth most prevalent global disease. Acne vulgaris occurs mainly during adolescence, due to hormonal changes, but also affects up to 64% of young adults, where the increase in body fat mass could, consequently, lead to insulin resistance and obesity[5]. The main etiological factors, currently accepted in the literature, are genetics (heredity), age (hormonal changes in adolescence), physical condition (body composition and insulin resistance) and, recently, nutrition (diet, supplementation and phytotherapy). Among these, physical condition and nutrition are the possibly modifiable factors. Individuals with increased fat mass and reduced fat-free mass may, through physical activity, exercise and nutrition, modify body composition, reduce systemic inflammatory status and improve, for example, insulin resistance[6]. The classic treatments for acne vulgaris are diverse, including, mainly, antibiotics and reducers of the sebaceous production (oral and topical). These are efficient, but may also allow relapse, and can lead to various adverse effects and nutritional impairments in the

body, such as intestinal dysbiosis, blood loss of cobalamin, folic acid and alpha tocopherol, resistance to other antibiotics, xerosis, cheilitis, alopecias, onicopathies and general dryness of the skin, among others. In this context, nutrition has been indicative of possible beneficial interactions, in conjunction with synthetic allopathic drugs, and direct effects on the lesions observed in the clinic[3,7,8,9,10,11]. The evidence correlating nutrition and dermatology is still scarce, but it already suggests possible clinical interventions. Given this context, the aim of this article is to review the literature on dietary interventions for the treatment of acne vulgaris in order to support the development of more effective and safe treatments in clinical practice.

2 METHODS

We carried out a systematic review of the literature from clinical trials over the last five years available in *PubMed* and *SciELO*. The descriptors used were: *Acne vulgaris, Propionibacterium acnes, acne treatment, acne diet, acne oil, acne nutrition, acne nutrients, acne food, acne supplements, green tea acne, omega-3 acne, fatty acids acne*. Articles that addressed oral nutrition were included in the study and repeated ones were excluded. The selected articles were analyzed according to the Jadad scale (1996), CONSORT (2010) and Cochrane by two researchers, independently. A general analysis of each clinical trial was carried out, including article title, author and year, scientific journal, impact factor, experimental design, randomization, blinding structure type, placebo control, sample number, gender, ethnicity, age, intervention and type of control, duration, methods used in the analysis, significant results and risk of bias. After the initial analysis, the Jadad scale was used to evaluate the quality of the articles using parameters such as randomization, proper execution and blinding. We used a three-point questionnaire, which attributes a single point for positive answers. There is also the possibility of an additional single point. The latter may lower the score of articles that have negative answers. The CONSORT (Consolidated Standards of Reporting Trials) checklist was used for classification, in which all the questions in the protocol were maintained and, for each evidence analyzed, a final percentage of positive responses was considered. The risk of bias, using the Cochrane protocol, analyzes "random sequence generation", "concealment of allocation", "blindness of participants and professionals", "blindness in the evaluation of results", "incomplete outcome data" and "selective results"[12,13,14]. Figure 1 (below) summarizes the main steps in the systematization process of this review.

Figure 1. Summary of the main systematizing steps of this review.



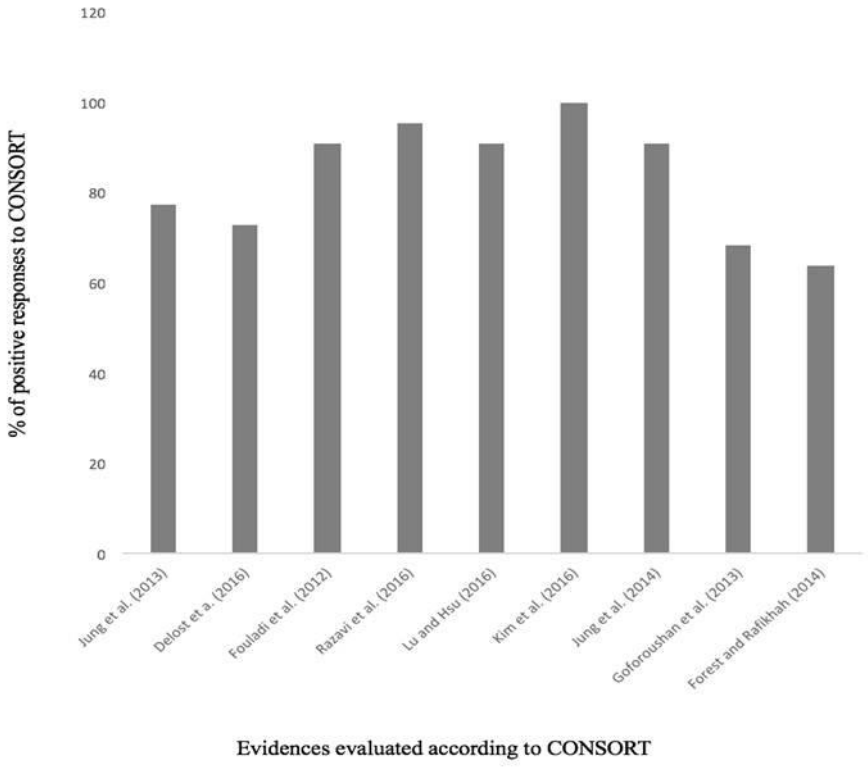
3 RESULTS AND DISCUSSION

The articles were analyzed using the Jadad and CONSORT tools. From these tools, with the values obtained in the Jadad scale, the graph was assembled to express the highest scores and qualities of the evidence. The percentages of positive answers were obtained from the CONSORT checklist. The evidence found in the studies with higher scores and percentages, according to the methods used, would be considered as the best

study designs and results.

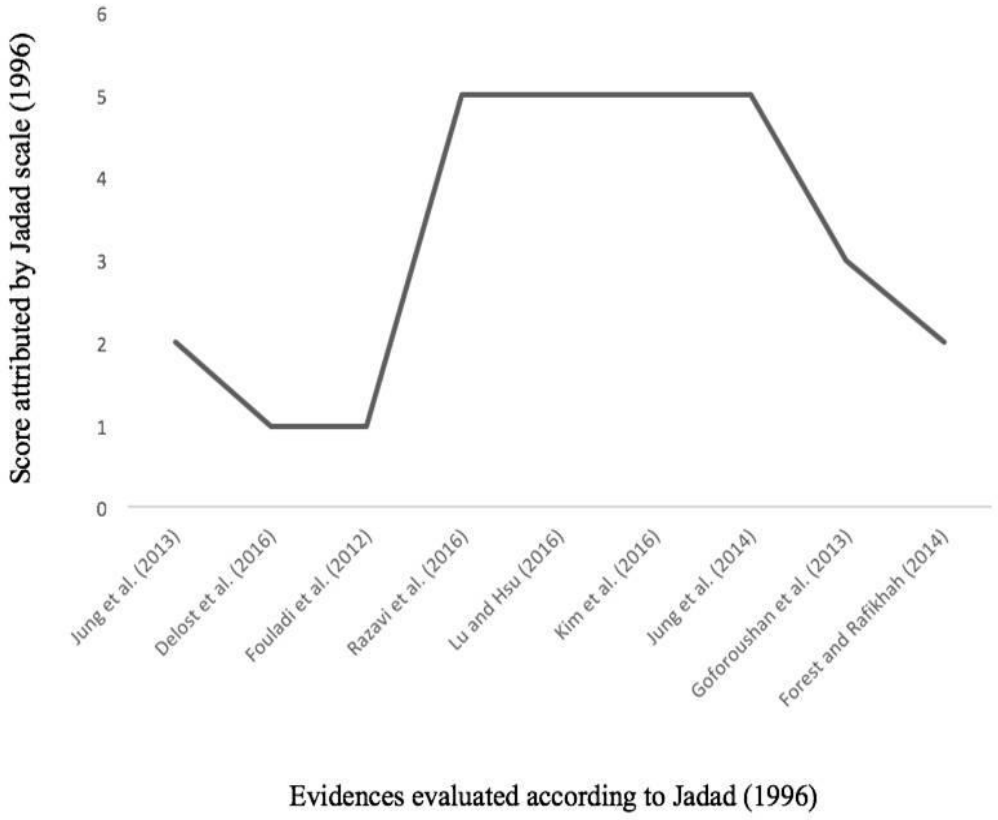
The CONSORT results showed that most of the evidence score was attributed in the titles, abstract and some of the methods. Regarding the methods, some parts need more detail, which contributed to the lower observed score among the evidences, expressed as a percentage. The parts of the method with little information included "who enrolled participants and who assigned interventions", "how blinding was done and who was blinded", "whether there was a placebo group, recording the similarities of interventions" and "enrollment and name of the clinical study recorded on the Clinical Trial website". The evidence that had the highest percentages were[15,16,17,18,19]. The results, in percentages, are shown in Figure 2.

Figure 2. Percentage of positive responses, after an analysis of scientific evidence, using the CONSORT (2010) protocol.



The results, after using the classic Jadad scale, presented a similar profile to that obtained with the CONSORT protocol. However, this tool is limited to detailing randomization and blinding. The study by Fouladi et al. (2012) did not observe the same CONSORT profile because it does not detail the randomization and blindness of the study in their method. The Jadad scale deducts two points for the absence of these descriptions (figure 3).

Figure 3. Evidence evaluated according to the Jadad (1996) scale



Using the Cochrane methodology, the risk of bias was evaluated. The results corroborated the evaluations obtained using CONSORT checklist and Jadad scale. Table 1 presents the analysis, which is indicated by the following codes, representing the original method: (*) green, (**) yellow, (***) red. Thus, (*) risk of bias is reduced, (**) risk of bias is uncertain and (***) risk of bias is increased.

Table 1. Risk of bias according to Cochrane method

	GRS	AC	BPP	BER	IRD	RSR	TOTAL
Jung et al. (2013) (20)	*	***	***	***	*	*	12
Delost et al. (2016) (21)	*	*	**	**	*	*	8
Fouladi et al. (2012) (15)	*	*	*	**	*	*	7
Razavi et al. (2016) (16)	*	*	*	**	*	*	7
Lu and Hsu (2016) (17)	*	*	*	**	*	*	7
Kim et al. (2016) (18)	*	*	*	**	*	*	7
Jung et al. (2014) (19)	*	*	**	**	*	*	8
Goforoushan et al. (2013) (22)	*	*	**	**	*	*	8
Forest and Rafikhah (2014) (23)	*	*	**	**	*	*	8

GRS: generation of random sequence. AC: allocation concealment. BPP: blindness of participants and professionals. BER: blindness in the evaluation of the results. IRD: incomplete result data. RSR: record of selective results.

4 NUTRITION IN THE TREATMENT OF ACNE VULGARIS

4.1 N-3 FATTY ACIDS

Jung et al. (2014), in their univariate, but not placebo controlled trial, conducted the study with a sample of 45 korean men and women volunteers between 18 and 33 years of age. One group received eicosapentaenoic acid (EPA - 500 mg) and docosahexaenoic acid (DHA - 500 mg) and another received borage oil (1000 mg borage oil with gamma linolenic acid - 200 mg) for a period of 10 weeks. The variables analyzed were: number of lesions, severity, subjective assessment of acne, histopathology, immunohistochemistry and adverse effects. Significant results were the number of inflammatory lesions (n3: 10.1 ± 3.2 to 5.8 ± 3.4, $P < 0.05$; gamma linolenic acid: 9.8 ± 5.2 to 6.6 ± 3.7, $P < 0.05$); noninflammatory (n3: 23.5 ± 9.2 to 18.9 ± 8.3; gamma linolenic acid: 22.8 ± 8.4 to 19.2 ± 7.2, $P < 0.05$); no significant differences between interventions were found in acne severity (n3: 2.4 to 1.7; gamma linolenic acid: 2.3 to 1.8); subjective evaluation (n3: 10.0 to 6.5; gamma linolenic acid: 10 to 6.8; $P < 0,05$); histopathology (n3: 2.1 to 1.6; gamma linolenic acid: 2.0 to 1.6, $P < 0.05$); IL-8 (n3: 1.9 to 1.5; gamma linolenic acid: 1.8 to 1.4). A small number of volunteers reported gastrointestinal discomfort and diarrhea, which improved in a few days (table 2) [19].

4.2 CAMELLIA SINENSIS

Lu and Hsu (2016) conducted a randomized, double-blinded and placebo-controlled clinical trial with a sample of 64 Chinese women between 25 and 45 years of age. The treated group received 1,500 mg of *Camellia sinensis* dry extract (57% epigallocatechin 3 gallate) and the placebo group received cellulose for a period of 4 weeks. The parameters analyzed were: body mass, blood pressure, heart rate, biochemical and clinical measures and acne lesions. The results indicated a reduction of total cholesterol in the group treated with *Camellia sinensis* ($P < 0.003$) and lesion counts in the forehead area ($P < 0.04$). The same authors cited another study using a sample of 80 women who received extract of decaffeinated *Camellia sinensis*. Thus, caffeine is probably not be involved in the improvement of acne vulgaris lesions. The results obtained were similar to those previously mentioned. Forest and Rafikhah (2014) also conducted a randomized clinical and placebo-controlled trial with 34 Iranian men and women between 12 and 17 years of age. They treated one group with a dry extract of *Camellia sinensis* (1,500 mg / day) and the placebo group received lactose, both for a period of 4 weeks. After the treatment period, there was a significant reduction in the

inflammatory lesions before and after the treatment period ($P < 0.001$), when compared to the placebo group ($P < 0.01$) (table 2) [17,23].

4.3 BERBERIS VULGARIS

Fouladi (2012) conducted a randomized, double-blind and placebo-controlled clinical trial with 49 Iranian men and women participants between 12 and 17 years of age. One group received 600 mg of aqueous extract of the *Berberis vulgaris* and the placebo group received lactose for a period of 4 weeks. Statistically significant results indicated that the intervention group, before and after 4 weeks, had reduced non-inflammatory lesions from 20.10 to 11.08 ($P < 0.001$) and inflammatory lesions from 24.28 to 13.24 ($P < 0.001$) (table 2) [15].

4.4 CHOCOLATE

Delost et al. (2016) also conducted a clinical trial with 54 North American men and women volunteers with mean age of 21.4 years. The objective was to evaluate the effect of milk chocolate (43 grams) on the pathogenesis of acne vulgaris. The control group received jelly beans (15 units), only as control and not as a placebo. The duration of the study was 4 weeks and the data evaluated were number of lesions and photographs. Significant results showed the chocolate group with 4.8 lesions ($P < 0.0001$), compared to the jelly beans group, with less 0.7 lesions (table 2) [21].

4.5 CHEONGSANGBANGPOONG-TANG

Kim et al. (2016) conducted a randomized, double-blinded and placebo-controlled clinical trial with 56 Korean men and women volunteers of 19 years of age. The intervention group received 5 g of Cheongsangbangpoong-tang granules and the control group received a mixture of lactose powder (95.2%), dextrin (2.94%), aromatic herbs (0.7%) and food coloring (1.16%) for a period of 8 weeks. Following the intervention they observed a significant reduction of the inflammatory lesions (intervention: - 32.4 ± 44; control: - 15.1 ± 44.9, $P < 0.05$) (table 2) [18].

4.6 CHROME AND SELENIUM

Jamilian et al. (2016) conducted a randomized, double-blinded, placebo-controlled clinical trial with Iranian women with polycystic ovary syndrome. The women received chromium supplementation (200 mcg) for a period of 8 weeks. After this period,

results indicated statistical significance for the prevalence of acne vulgaris (20.0 / - 3.3%, *P* = 0.04). Similarly, Razavi et al. (2016), in the same year, conducted a randomized, double-blinded, placebo-controlled clinical trial with 64 Iranian women between 18 and 40 years of age with acne caused by polycystic ovary syndrome. The treated group received 200 mcg of selenium and the placebo group received cellulose for a period of 8 weeks. Significant results indicated a reduction of acne vulgaris after the treatment period (46.9 - 12.5%; *P* = 0.003) (table 2) [16,24].

4.7 OTHER SUPPLEMENTS FOR TREATING ACNE VULGARIS

Shalita et al. (2012) studied a nutritional supplement, composed of nicotinamide, zinc, pyridoxine, copper and folic acid among patients with acne vulgaris. The study was designed as a non-randomized, non-blinded and non-placebo-controlled clinical trial. The study involved 235 men and women participants from North American. The group received between 1 and 4 tablets (composition of the tablets: azerizine 700 mg, zinc 12 mg, pyridoxine 8 mg, copper 2 mg, folic acid 500 mcg) for a period of 8 weeks. After the treatment, the severity of inflammatory acne vulgaris lesions was analyzed and significant results indicated an 88% reduction of inflammation and an 81% improvement in skin appearance with acne vulgaris following the full treatment period (table 2) [25].

Fabbrocini et al. (2016) conducted a non-blinded, non-placebo-controlled clinical trial with 30 young Italian men to test the hypothesis that the nutritional supplement [2000 mg (myoinositol) + 56.25 mg (liposomal magnesium) + folic acid] could be used in the treatment of acne vulgaris. The control group was given an antibiotic and isoenergetic diet (without placebo control). The data evaluated was obtained from the analysis of photographs, anthropometry and biochemical tests. Significant results indicated that there was an improvement in the metabolic profile and insulin resistance among the subjects that presented biochemical changes early in the treatment (table 2) [26].

Similarly, Formuso et al. (2015) studied a nutritional supplement with myoinositol and D-chiro inositol. The clinical trial was placebo-controlled and involved 137 women of childbearing age for a period of 24 weeks. The variables analyzed were menstrual cycles, anthropometry, number of acne lesions and biochemistry. Significant results included improved menstrual cycles, weight gain, insulin resistance and reduced acne lesions (table 2) [27].

Table 2. Important variables in the clinical trials for the treatment of acne vulgaris

Author / Year	N	Sex	Nationality	Age (years)	Treatment	Duration (weeks)	Main Results
Jung et al. (2013) (20)	45	f	Canadian	18 – 35	Probiotics and minocycline	12	Reduction of lesions in all groups (4 wk; $P < 0.001$). Group probiotics + minocycline reduced (12 wk) and was more significant than the isolated probiotic group ($P < 0.001$) and minocycline alone ($P < 0.01$).
Delost et al. (2016) (21)	54	m/f	North American	21.4	Chocolate (43 g)	4	Chocolate (+ 4.8 lesions) $P < 0.0001$; jelly beans (- 0.7 lesions).
Fouladi et al. (2012) (15)	49	m/f	Iranian	12 - 17	*Berberis vulgaris* (600 mg AE)	4	Intervention group (before and after 4 wk: 20.10 to 11.08 – $P < 0.001$ - noninflammatory; before and after: 24.28 to 13.24 - $P < 0.001$ - inflammatory); Intervention x control 4 wk ($P < 0.001$).
Razavi et al. (2016) (16)	64	f	Iranian	18 – 40	200 µg	8	Pregnancy rate: 18.8% (6/32) x 3.1% (1/32), $P = 0.04$; reduction: alopecia (40.6 x 9.4%, $P = 0.004$) and acne vulgaris (46.9 x 12.5%, $P = 0.003$).
Lu and Hsu (2016) (17)	64	f	Chinese	25 – 45	*Camellia sinensis* (DE) - 1,500 mg - 57% EGCG	4	Reduction in total lesions - CS group $P < 0.003$; number of forehead lesions ($P < 0.04$).
Kim et al. (2016) (18)	56	m/f	Korean	> 19	Cheongsangbangpoong-tang (5 g)	8	Reduction of inflammatory lesions (intervention: - 32.4 ± 44, control: -15.1 ± 44.9) $P < 0.05$.
Jung et al. (2014) (19)	45	m/f	Korean	18 – 33	1: 500 mg EPA + 500 mg DHA; 2: 1,000 mg borage oil with 200 mg	10	Number of inflammatory lesions (Omega

					of gamma linolenic acid		3: 10.1 ± 3.2 to 5.8 ± 3.4, *P* < 0.05); GLA: 9.8 ± 5.2 to 6.6 ± 3.7, *P* < 0.05); noninflammatory Omega 3: 23.5 ± 9.2 to 18.9 ± 8.3; GLA: 22.8 ± 8.4 to 19.2 ± 7.2, *P* < 0.05); no difference between interventions; acne severity (omega 3: 2.4 to 1.7; GLA: 2.3 to 1.8); subjective evaluation (omega 3: 10 to 6.5, GLA: 10 to 6.8, *P* < 0.05); histopathology (omega 3: 2.1 to 1.6; GLA: 2.0 to 1.6, *P* < 0.05); IL-8 (omega 3: 1.9 to 1.5, GLA: 1.8 to 1.4).
Goforoushan et al. (2013) (22)	60	m/f	Iranian	21	Treatment: isotretinoin (0.5 mg / kg) + 800 IU vit E; Control: isotretinoin (0.5 mg / kg) + cod liver oil free vit E	6	Reduction of dermatological signals in the intervention group, sixth week (*P* < 0.037).
Forest and Rafikhah (2014) (23)	34	m/f	Iranian	12 – 17	1,500 mg *Camellia sinensis* (DE)	4	Significant reduction of inflammatory lesions (*P* < 0.001) before and after treatment, compared to the control group (*P* < 0.01).
m: male; f: female; vit: vitamin; wk: weeks; g: gram; mg: milligram; µg: microgram; kg: DE: dry extract; AE: aqueous extract; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; IL-8: interleukin 8; GLA: gamma linolenic acid.							

5 NUTRITION AND ADVERSE EFFECTS IN MEDICINAL TREATMENT FOR ACNE VULGARIS

5.1 ALPHA-TOCOPHEROL

Goforoushan et al. (2013) conducted a randomized, placebo-controlled clinical trial with 60 Iranian men and women participants of approximately 21 years of age. The treated group received isotretinoin (0.5 mg / kg) and vitamin E (800 IU) and the placebo

group received isotretinoin (0.5 mg / kg) and cod liver oil (vitamin E free) for a period of 6 weeks. The authors evaluated skin and mucous membrane lesions, adverse effects and influence on the blood concentrations of vitamin E. Statistically significant results indicated a reduction in adverse events in the skin and mucosa among the intervention group (with vitamin E) after the sixth week of treatment ($P < 0.037$) [22].

5.2 PROBIOTICS

Probiotics were considered in the study by Jung et al. (2013) in a randomized, non-blinded, non-placebo controlled clinical trial with 25 Canadian women between 18 and 35 years of age. They were divided into three treatment groups: minocycline + probiotic, only minocycline and only probiotic for a period of 12 weeks. After the treatment period, the lesions were counted. The following results showed statistical significance: lesion reduction in all groups after 4 weeks ($P < 0.001$). After 12 weeks, the minocycline + probiotic group had more significant reductions, compared to the only probiotic group ($P < 0.001$) and only minocycline group ($P < 0.01$). The data suggests that there is a synergism between the nutritional supplement and drug, with advantages for the treatment of acne vulgaris, with a possible reduction of adverse effects and improved quality of life of patients[20].

5.3 MIXTURE OF NUTRIENTS AND PHYTOCHEMICALS

Fabbrocini et al. (2014), in a randomized, non-controlled clinical trial with 48 Italian men and women volunteers gave the experimental group a supplement containing isotretinoin and antioxidants (components: gamma linolenic acid, vitamin E and C, beta carotene, coenzyme Q10 and *Vitis vinifera*). The control group received only isotretinoin (20-30 mg/day) for a period of 24 weeks. The authors analyzed the global acne grading system (GAGS) and evaluated the production of sebum and corneometry. Significant results indicated a reduction of side effects of the medication, a reduction of skin and mucosa dryness, improved hydration and a greater adherence to medication as a therapy. Results suggest that nutrition may have a fundamental function in the tolerance of drug treatment and, therefore, influence on the duration of treatment and reduction of financial costs for these drugs[26].

6 DRUGS FOR ACNE VULGARIS AND NUTRITIONAL IMPAIRMENTS

6.1 FOLIC ACID AND COBALAMIN

Kamal and Polat (2015) conducted a case-control study with 62 Turkish participants, of both genders, over 18 years of age. Volunteers with moderate to severe acne vulgaris were monitored, as well as a control group with the same number of healthy individuals. Participants with acne vulgaris took isotretinoin (0.5 or 1.0 mg / kg) for a period of 45 days. The authors analyzed changes in the blood of patients by chemiluminescence (immunoassay) and found an increase in homocysteine concentrations, before and after treatment, in the group 0.5 mg / kg / day of isotretinoin (values between 7 and 8; $P < 0.018$) and in the group 1.0 mg / kg / day of isotretinoin (values between 6 and 8; $P < 0.003$). Total cholesterol increased from 148.1 to 164.4 mg / dL ($P < 0.002$), in the group 1.0 mg / kg / day of isotretinoin. Triglyceride levels indicated significant variation, also, for both isotretinoin dosages. In the group taking 0.5 mg / kg / day of isotretinoin, levels increased from 75 to 77 mg / dL ($P < 0.001$) and among individuals taking 1.0 mg / kg / day of isotretinoin, triglyceride values increased from 90 to 98 mg / dL / day ($P < 0.002$). Javanbakht et al. (2012), in their non-randomized, non-blinded, placebo-controlled clinical trial with 61 Iranian men and women (with a mean age of 23.6 years) treated volunteers with isotretinoin (0.5 mg / kg) for a period of 4 weeks. Following treatment, there was a significant reduction in folic acid concentrations in the blood, from 26.75 nmol / L to 23.6 nmol / L ($P = 0.008$), corroborating the previous findings[30].

Taking into consideration that some patients were overweight or obese, with insulin resistance and/or type 2 diabetes *mellitus* when in treatment for acne vulgaris, nutritional deficiency damages could contribute to an increased susceptibility to cardiometabolic risks. This indicates that nutrition may be important during drug treatments to reduce these risks. Furthermore, there are some patients who cannot use these drugs due to limitations, such as pregnancy.

6.2 ALPHA-TOCOPHEROL

Aktürk et al. (2013) also observed changes in the nutritional status of participants after medication. They conducted a non-randomized, non-blinded, placebo-controlled clinical trial with 46 Turkish men and women participants. The experimental group received isotretinoin (0.6 - 0.8 mg / kg / day) until reaching the final cumulative dose (120 mg / kg / day) for a period of 7 weeks. After the treatment period, blood vitamin E was evaluated and indicated a significant reduction, from 20.22 to 16.24 mg / dL, corroborating the previous findings. These changes suggest a correlation between the use of isotretinoin for the treatment of acne vulgaris and increased oxidative stress. This,

therefore, being responsible for the adverse effects of the medication[32].

7 LIMITATIONS OF SCIENTIFIC EVIDENCE INVOLVING NUTRITION AND ACNE VULGARIS

The scientific evidence involving nutrition and acne vulgaris is scarce and there is a heterogeneity between variables, suggesting, therefore, relevant limitations in methods. This fact restricts, for example, a quantitative summary of the variables. However, this does not preclude a descriptive and analytical review.

Some clinical trials are not controlled or do not have a placebo control. Consequently, there is the placebo effect. Thus, the subtration of its influence would result in more real results. Most of the studies involve Iranian, Chinese and Korean subjects. A few involve North Americans, Canadians and Italians. Other populations in the world have not been adequately studied and included in the development of epidemiological indicators, such as morbidity and mortality among Western populations, suggesting an increase in the prevalence of chronic noncommunicable diseases and/or lack of access to care, health and reduced social development, for example. Some studies included in this review involved individuals from a wide age group. This could limit, for example, correlations between critical stages of development, such as hormonal differences between adolescent and adult subjects. The intervention treatments are composed of many compounds and, for this reason, it is very difficult to consider nutrients or non-nutrients and relevant modulatory mechanisms associated with the improvement of the elemental lesions of the skin. The methods usually employed in clinical studies are economical in their correlations with complete anamnesis, physical, anthropometric and dietary evaluation.

There is a need to increase the quantity and quality of scientific evidence with respect to the nutritional treatment of acne vulgaris in order to more effectively and safely guide the nutritional actions of clinical practice today.

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