

DIETARY AND PHARMACO-THERAPY IN SKIN DISEASES

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Abstract

Regardless of age and pathology, skin diseases are a public health problem, influencing the quality of patients' life. Complementary to drug treatment, dietary treatment has been shown to be an effective adjunct in the amelioration or treatment of dermatological conditions. In this paper we aim to review the researches published in 2019 - 2022 on dietary treatment in skin diseases. Our study is a systematic review. The PubMed, Web of Science and NAMMDR (National Agency for Medicines and Medical Devices of Romania) databases were analysed. The search criteria were acne, allergic dermatitis, chronic urticaria and dietary treatment in skin diseases. There are numerous studies that demonstrate the importance and effectiveness of dietary treatment in dermatological pathology. For the acne vulgaris case, essential oil and bergamot juice, respectively those of sweet oranges, represent an effective dietary therapy by inhibiting the secretion of sebaceous glands and the release of IL-1 α , stimulating apoptosis in the sebaceous glands. Other foods that are effective in treating skin diseases are: pasteurized and enhanced cow's milk with alkaline phosphatase, probiotics, Korean red ginseng or probiotics for atopic dermatitis. In the case of psoriasis, the effective dietary treatments are: curcumin, green tea, coffee, *Calendula officinalis* L, *Origanum vulgare*, *Satureja hortensis* L, *Allium sativum*, *Anethum graveolens* L. In the case of alopecia areata, the dietary treatment with ginger (*Zingiber officinale*) had very good results. Food supplements based on selenium, vitamins A, C, E, zinc, manganese, copper and coenzyme Q10, are a variant with obvious clinical results in dermatology. Dietary treatment of skin diseases is a real complementary method. For high efficacy, due to the complexity of possible causes, the composition of foods or dietary supplements, as well as possible side effects, diagnosis and therapy must be approached multidisciplinary.

Rezumat

Indiferent de vârstă și patologie, bolile de piele reprezintă o problemă de sănătate publică, influențând calitatea vieții pacienților. Complementar tratamentului medicamentos, tratamentul dietetic s-a dovedit a fi un adjuvant eficient în ameliorarea sau tratamentul afecțiunilor dermatologice. În această lucrare ne propunem să analizăm cercetările publicate în 2019 - 2022 privind tratamentul dietetic în bolile de piele. Studiul nostru este o sinteză sistematică. Au fost analizate bazele de date PubMed, *Web of Science* și Agenția Națională a Medicamentului și Dispozitivelor Medicale din România. Criteriile de căutare au fost acnea, dermatita alergică, urticaria cronică și tratamentul dietetic în bolile de piele. Există numeroase studii care demonstrează importanța și eficacitatea tratamentului dietetic în patologia dermatologică. Pentru cazul acneei vulgare, uleiul esențial și sucul de bergamotă sau de portocale dulci, reprezintă o terapie dietetică eficientă prin inhibarea secreției glandelor sebacee și eliberarea IL-1 α , stimulând apoptoza în glandele sebacee. Alte alimente care sunt eficiente în tratarea bolilor de piele sunt: laptele de vacă pasteurizat și îmbunătățit cu fosfatază alcalină, probiotice, ginseng roșu coreean sau probiotice pentru dermatita atopică. În cazul psoriazisului, tratamentele dietetice eficiente sunt: curcumina, ceai verde, cafea, *Calendula officinalis* L, *Origanum vulgare*, *Satureja hortensis* L, *Allium sativum*, *Anethum graveolens* L. În cazul alopeciei areata, tratamentul dietetic cu ghimbir (*Zingiber officinale*) a avut rezultate foarte bune. Suplimentele alimentare pe bază de seleniu, vitaminele A, C, E, zinc, mangan, cupru și coenzima Q10, sunt o variantă cu rezultate clinice evidente în dermatologie. Tratamentul dietetic al bolilor de piele reprezintă o adevărată metodă complementară. Pentru o eficacitate ridicată, datorită complexității cauzelor posibile, compoziția alimentelor sau suplimentelor alimentare, precum și posibilele efecte secundare, diagnosticul și terapia trebuie abordate multidisciplinar.

Keywords: acne, allergic dermatitis, chronic urticaria, diet, nutraceutical

Introduction

Regardless of age and pathology, the dermatological conditions are a public health problem that can induce a decrease on quality of life, through the appearance

of anxiety, low self-esteem, depression and even suicide attempts. Diet plays an important role in the management of skin diseases, but sometimes it is difficult to separate evidence-based facts from circulating myths

(because some nutrients are difficult to measure and complex inter-food interactions are difficult to assess). The list of skin diseases influenced by diet is long: from herpetiform dermatitis from celiac disease to acne vulgaris, contact dermatitis, urticaria, psoriasis, those genetically coordinated (phenylketonuria, tyrosinaemia, galactosaemia, porphyria, gout) or food-induced (kwashiorkor, scurvy, pellagra, marasmus) or excesses (lycopenaemia-tomatoes or carotenaemia-carrots). In addition, dermatological diseases are closely related to diet and microbiome, for this reason the main solution is the effective association between personalized diet, individual food diary and dietary supplements to balance the intestinal flora.

The number of people informed about the role of lifestyle, quality diet and implicitly its supplementation with minerals, vitamins, fibre, polyphenols, antioxidants, etc., has led to the development of the food supplement industry, “clean label” and/or organic foods. Regardless of age, the health-beauty tandem is valid for both sexes, both women and men being aware that the external appearance is based on the internal aspect or health, respectively diet and lifestyle. Thus, the last years have registered the development of a new range of products - nutricosmetics. In “Marine-Derived Compounds with Potential Use as Cosmeceuticals and Nutricosmetics” [4], Ana Alves *et al.*, eloquently presents the definition of nutricosmetics as “natural health products with the ability to improve the function and appearance of skin, hair and nails when ingested” [4]. In the same paper, Alves *et al.* showed the difference between nutraceuticals and cosmeceuticals, the latter being a combination of “cosmetics” and “pharmaceuticals” [4]. For this reason, the nutricosmetics industry is and will be constantly developing. The causes that can lead to skin diseases such as acne, allergic dermatitis and chronic urticaria are numerous. These can be psychosomatic, food (gluten, dairy, refined sugars, tomatoes, alcohol, or large amounts of foods high in D-galactose, processed foods), genetic, endocrinological, microbiological, immunological [24]. In addition to food, acne has also been caused by dietary supplements containing vitamins B6, B12, iodine or dietary supplements with whey and anabolic-androgenic steroids (ASA) [19]. Another possible cause is the dermatological adverse reaction (AR) following the improper application of topical treatment for atopic dermatitis [22].

According to the characteristics of the products available on the Index of Medicinal Products for Human Use and Summary of product characteristics website in December 2020, due to the excipients contained or the active substances, topical dermatological treatments for the treatment of atopic dermatitis (AD) may cause or aggravate rosacea and/or acne vulgaris, being contraindicated in the treatment of this condition. The active substances that can activate/aggravate these types of acne are: high potency corticosteroids:

betamethasone (e.g. Advantan 1 mg/g[®] ointment, cream, skin emulsion, Betaderm[®] cream, ointment, Ekarzin 0.5 mg/g[®] cream); mometasone (e.g. Elocom 1 mg/g[®] cream, ointment); very potent corticosteroids: clobetasol (e.g. Clobetasol MK 0.5 mg/g[®] ointment, Dermovate 0.5 mg/g[®] cream, ointment), fluticasone propionate (e.g. Cutivate 0.05 mg/g[®] ointment, Cutivate 0.5 mg/g[®] cream); high potency corticosteroids in other combinations: betamethasone as dipropionate and clotrimazole (e.g. Clo-Ekarzin 0.50 mg/10 mg[®] cream), betamethasone and form betamethasone dipropionate and gentamicin as gentamicin sulphate (e.g. Diprogenta 0.5 mg/1 mg *per gram*[®] ointment, cream), betamethasone dipropionate and salicylic acid (e.g. skin solution – Diprosalic 0.64 mg + 20 mg/g[®], ointment – Diprosalic 0.64 mg + 30 mg/g[®]); anhydrous fusidic acid as fusidic acid hemihydrate and betamethasone as betamethasone valerate (e.g. cream Fucidin H[®]), betamethasone as dipropionate and salicylic acid (e.g. ointment - Sal-Ekarzin 0.50 mg/30 mg *per gram*[®]), betamethasone dipropionate, gentamicin sulphate and clotrimazole (e.g. cream – Tresyl[®]), low potency glucocorticoids in combination with antibiotics for dermatological use: anhydrous fusidic acid in the form of fusidic acid hemihydrate and hydrocortisone acetate (e.g. cream Fucidin H[®]), moderate corticosteroids: hydrocortisone butyrate (e.g. cream Locoid[®], Locoid Lipocream[®]), or even corticosteroids with moderate potency in combinations: triamcinolone acetonide, neomycin sulfate, nystatin (e.g. cream Nidoflor[®]).

Topical excipients for the treatment of AD that may cause local skin side effects such as contact dermatitis are: cetylstearyl alcohol (Advantan 1 mg/g[®] ointment, cream, Betaderm[®] cream, ointment, Diprogenta[®] cream, Ekarzin 0.5 mg/g[®] cream, Fucidin H[®] cream, Tresyl[®] cream); butylhydroxytoluene – E 321 (e.g. Advantan – 1 mg/g[®] ointment, cream), cetyl alcohol (cream Nidoflor[®], Ekarzin[®] cream – 0.5 mg/g[®] cream, Fucidin H[®] cream), butylhydroxyanisole and potassium sorbate (e.g. Fucidin H[®] cream). Allergic reactions (even delayed) may be caused by the excipients: p-hydroxy methyl – E 218 (Nidoflor[®] cream, Tresyl[®] cream), n-propyl p-hydroxybenzoate – E216 (Locoid[®] cream, Locoid Lipocream[®], Tresyl[®] cream). Allergic reactions as well as local irritation of medium intensity are caused by benzyl alcohol (e.g. Advantan Milk 1 mg/g[®] skin emulsion, Ekarzin 0.5 mg/g[®] cream) or chlorocresol (e.g. Fucidin H[®] cream, Betaderm[®] cream). Skin irritation may be caused by excipient moisturizers: propylene glycol – E 1520 (e.g. Clobetasol MK 0.5 mg/g[®] ointment, Cutivate 0.05 mg/g[®] ointment, Cutivate 0.5 mg/g[®] cream, Dermovate 0.5 mg/g[®] cream, Dermovate 0.5 mg/g[®] ointment, Dermovate 0.5 mg/g[®] skin solution, Ekarzin 0.5 mg/g[®] cream, Nidoflor[®] cream).

According to researchers Zami DH *et al.* [29], in addition to topics with corticosteroids, the acne can be

caused by hormonal drugs, lithium, antituberculosis, halogens, iodine and bromine, respectively drugs against cancer, immunosuppressants and those for autoimmune diseases.

Other drugs that can cause dermatological side effects are: chemotherapeutic agents (epidermal growth factor receptor inhibitors (EGFRs)) used in cases of organ malignancy – most side effects have been acne rash [3], antidepressants (vortioxetine) [13], psychotropic drugs [28], the potential COVID-19 drugs [25], anticancer therapies based on immune checkpoint inhibitors [17]. In this paper we aimed to review the researches published in 2019 - 2022 on dietary treatment in skin diseases, as a complementary therapeutic method.

Materials and Methods

The PubMed and NAMMDR databases on topical drugs for the treatment of AD and which are authorized for placing on the market were analysed. The search criteria were acne, allergic dermatitis, chronic urticaria and dietary treatment in skin diseases. The side effects of dietary treatments included in the treatment of the aforementioned pathologies were also sought.

Results and Discussion

Foods whose systemic immunoregulatory effect has been determined pre-clinically are shown in Table I and Tables II and III, respectively, are foods/substances whose efficacy has been determined clinically.

Table I

Foods whose systemic immunoregulatory effect in the treatment of skin diseases has been pre-clinically determined

The product/ preparation, dose, mode of administration	Preclinical determinations of food efficacy						
	Pathology followed	Species/ line, sex, age (weeks)	No. animals/ no. group	Period/ no. days	The mechanism of inducing the pathology	The main action that was monitored and demonstrated	The mechanism of action of food
Bergamot* (essential oil and juice) and sweet orange* (juice and essential oil)* [21]	A.v*	<i>Mesocricetus auratus</i> (Golden Hamsters) [21]	80/10 [21]	28 [21]	Excessive androgen secretion [21]	- Secretion of sebaceous glands* ↓; - Inhibition of TG accumulation; - Release IL-1α ↓; - IL-6 ↓; - Apoptosis in the sebaceous glands ↑; - T/E2* ↓; - caspase-3 ↓; - Adverse effects on testicular and spleen indices: none [21]	- Activating the expression of apoptotic proteins with reduction of area or thickness sebaceous glands; inhibition of caspase-3 attenuates the proliferation of sebaceous gland cells and organ size; anti-inflammatory effect [21]
Cow's milk pasteurized and enhanced with ALP*, 0.5 mL, oral [2]	Allergy	Mice C3H/HeOuJ/ females/3 weeks [2]	48/6 [2]	28 [2]	20 mg chicken egg protein dissolved in 0.5 mL PBS* containing 10 µg CT* for 5 days; 0.5 mL of raw milk, for 8 days consecutive [2]	- IgE ↓; - Th2 ↓; - IL – 13 ↓; - CD103 ↑; - CD11b ↑; - DC ↑; - TGF-β ↑ [2]	- Allergy suppression: IgE ↓; Th2 ↓; IL – 13 ↓; CD103 ↑; CD11b ↑; DC ↑; TGF-β ↑ [2]
Apigenin, 150 mg/kg body weight, oral [6]	AD [6]	Mice ICR [6]	20/4 [6]	7 [6]	Compound 48/80, 50 µg injection for inducing scratch behaviour [6]	- IL - 31 ↓; - IL-31 release into HMC-1 cells; - Suppression of scratch behaviour [6]	- mARN IL-31 ↓ [6]
Korean red ginseng, capsules, 500 mg RG*/capsule (2.5 g/kg bw), oral (dissolving RG powder in water) [16]	AD [16, 29]	Mice SD*, males, 6 weeks [16]	20/4 [16]	27 [16]	Performing two round wounds with a diameter of 2 cm [16]	- Moisture in skin ↑; - Skin lipids ↑; - Angiogenesis ↑; - Epithelialization ↑; - Very active fibroblasts; - Collagen accumulation ↑; - Regeneration time ↓ [16]	- TGF-b1*↑; - VEGF* ↑; - MMP-1↑; - MMP-9↑ [16]

* ↑ - growth/stimulation; ↓ - decrease; Bergamot – *Citrus medica* L. var. *sarcodactylis*, administered doses: 14 mL/kg bw bergamot oil, 17.5 mL/kg bw bergamot juice, 0.21 mL/kg bw bergamot oil, 0.33 mL/kg bw bergamot juice; sweet orange – *Citrus sinensis* (L.) Osbeck: 14 mL/kg bw sweet orange oil, 17.5 mL/kg bw sweet orange juice, 0.21 mL/kg bw sweet orange oil, 0.33 mL/kg bw sweet orange juice; Av – acne vulgaris; T/E2 – serum levels T and E2; ALP – alkaline phosphatase; PBS – solution containing phosphate buffered saline; CT – cholera toxin; SD – Sprague-Dawley; TGF-b1 and VEGF – genes; MMP-1 – metalloproteinase 1 matrix; MMP-9 – metalloproteinase 9 matrix

Table II

Foods whose systemic immunoregulatory effect in the treatment of AD has been clinically determined

Active substance/ dose	The main action monitored and demonstrated	Mechanism of action of the drug/active substance	Side effects
L-92*/20 mg [13]	- Median value of SCORAD ↓; - Median value of drug scores ↓; - IDQOL* ↑ [13]	- Total IgE* ↓; - Th2 ↓; - TARC* ↓; - Lecithinase (-) Clostridium ↓; - <i>Enterobacteriaceae</i> ↓ [13]	Not

* L-92 – *Lactobacillus acidophilus* L-92; IgE – Immunoglobulin; TARC – thymus and activation-regulated chemokine; IDQOL – Dermatitis Quality of Life index; EASI – severity index score; VAS – Visual analogue scale; IGA – Investigator global assessment (Investigator's overall assessment)

Table IIIFoods/alternative treatments whose systemic immuno-regulatory effect in the treatment of AD has been determined *in vitro*

Active substance	The main action monitored and demonstrated
Duolac® ATP *, 2 × 10 ⁶ CFU/200 µL/day [18]	- Treg differentiation: CD4 + T ↑ proliferation, Foxp3 +/-Tregs ↑, IL - 10 ↑; - IFN-γ ↑, IL-4 ↓ [18]
Strawberry seed extract (tilirosida), 1.0 - 3.0 µg/mL [18]	- Synthesis of ceramides in the <i>stratum corneum</i> ↑, with the exception of ceramide [EOS], [AP]; - Skin barrier function and moisture retention ↑; - GCS and GBA ↑; - SPT2 and CerS3 – unaffected [18]
<i>L. sakei</i> WIKIM30, 2 × 10 ⁹ CFU, oral [18]	- DC and T cell modulation: • TNF-α ↑, IL-6 ↑, IL-12p70 ↑, IL-10 ↑; • CD40 ↑, CD69 ↑, CD80 ↑, CD86 ↑ and MHCII; • PD-L1 ↑ and CD103 ↑; • D4 + ↑, CD25 + ↑, Foxp3 + ↑, Tregs ↑; - Modulation of T cell immune responses: • Th2 ↓, IL - 4 ↓, IL - 10 ↑; • Improvement of AD specific lesions; • IgE ↓ [18]

* Duolac® ATP – probiotic preparation containing four strains of probiotics: *L. casei* CBT LC5 (KCTC12398BP), *L. plantarum* CBT LP3 (KCTC10782BP), *L. rhamnosus* CBT LR5 (KCTC12202BP) and *B. lactis* CBT BL3 (KCTC11)

In the case of golden hamsters, the treatment with orange essential oil could significantly decrease the growth rate of the sebaceous gland compared to the corresponding dose of juice groups ($p < 0.05$). Both groups of patients treated with essential oil or bergamot juice and those treated with orange or sweet orange essential oil reported the effect of lowering the growth rate of sebaceous glands with a dose-effect relationship [19]. In the case of IL-1α, it was found that bergamot juice decreased its' level to 1/5 of the IL-1α value of the control group. IL-1α was also lower in the case of orange essential oil compared to the group in which the orange juice was administered [19], similar to bergamot. IL-6 was lower in the low-dose groups of bergamot oil and high-dose sweet orange essential oil.

Functional foods and dietary supplements can be considered nutraceuticals. Considering the general principles of food development for special nutritional states, presented by Rotaru M *et al.* [18], we believe that they can be an important tool in the development of nutraceuticals.

Based on the etiopathogenesis of acne, the researchers Kurokawa and Nakase [10] believe that antioxidants, vitamin D analogues [5, 27] and antimicrobial peptides

are potential treatments for acne in the future, along with topical anti-androgens, melanocortin receptor antagonists, IGF-1 inhibitors, PPAR modulators, acetylcholine inhibitors, local retinoic and metabolic blocking agents, monoclonal antibodies, phosphodiesterase inhibitors, IL-1β inhibitors, dapson, systemic antiandrogens and immunotherapy.

Mieczan *et al.* found increased oxidative stress and low levels of vitamin A, α-carotene and vitamin E in patients with psoriasis. They recommend that patients' diets be of the anti-inflammatory type, with a low content of pro-inflammatory substances (arachidonic acid responsible for the appearance of inflammatory eicosanoids). The addition of curcumin and green tea to the diet will increase the total antioxidant status [27]. Other foods with anti-inflammatory properties are: coffee, medicinal plants – *Calendula officinalis* L rich in flavonols and flavonic glycosides, coumarins, sterols, carotenoids, *Origanum vulgare* with a high content of phenolic compounds (protoeic acid, caffeic acid and coumaric acid), *Satureja* (thyme) rich in phenolic compounds, especially carvacrol, thymol, monoterpenes (e.g. α-pinene, α-terpine, limonene, myrcene), dill – *Anethum graveolens* L, with strong

antioxidant properties determined by 7- α -hydroxymanool, 1-carvona, limonene, epi- α -bisabolol [27].

Due to its content in flavonoids and tannin, aqueous or alcoholic cinnamon extract improves the parameters of oxidative stress [27]. Another aqueous extract with very good results is the one obtained from *Allium sativum* (garlic). Fruits rich in antioxidants and flavonoids considerably reduce oxidative stress in patients with psoriasis (e.g. berries, plums, apples, pomegranates, etc.) [19, 27].

The efficacy in reducing oxidative stress in patients with psoriasis of dietary supplements based on selenium, vitamins A, C, E, zinc, manganese, copper and Q10 coenzyme, has also been shown clinically [27]. Also, in the case of psoriasis, Locker *et al.* determined the effectiveness of the ketogenic diet in reducing pro-inflammatory factors [11].

Daily consumption, for 8 days of yogurt containing the strain *Lactococcus lactis* 11/19-B1, by children with atopic dermatitis (DA), considerably improved the severity score of the disease (SCORAD) from 38.8 ± 14.4 at 24.2 ± 12 [22]. Other probiotics whose preclinical efficacy in reducing AD has been demonstrated are LP340 800 (LP340 – *Lactobacillus pentosus* bacteria, present in various fermented foods) [18], and ginger (*Zingiber officinale*) improve the oxidative stress and trace elements in patients with *alopecia areata* [1].

In order for drug and dietary treatment to be highly effective, given the complexity of the causes that can cause skin diseases, it is necessary to screen their use [14]. Chenj JL *et al.* considers that in addition to endogenous advanced glycation (AGE) end products, dietary AGEs (dAGE) from unprocessed or processed foods may be involved in food allergies [7]. Through the anthropometric evaluation and food frequency questionnaires, from the cross-sectional study conducted on psoriasis patients in Brazil, Polo TCF *et al.* [17] have shown that weight control can improve the prognosis of psoriasis and increase the quality of life. Caloric control also leads to significant improvements in skin lesions. Wu JY *et al.* [28] demonstrated for the first time the anti-inflammatory effect of chrysoeriol contained in *Lonicera japonica* Thunb, on the proteins phospho-p65 (Ser536), phospho-STAT3 (Tyr705), inducible nitric oxide synthases (iNOS), cyclooxygenase-2 (COX-2), interleukin 6 (IL-6), IL-1 beta and tumour necrosis factor alpha (TNF-alpha), preclinical model. In the review, Islam *et al.* [9] showed that the symptoms of systemic lupus erythematosus autoimmune disease are alleviated with a low-calorie, low-protein diet, high in fibre, polyunsaturated fatty acids, vitamins, minerals and polyphenols. Two anti-inflammatory and anti-pruritic acids with anti-AD action are conjugated linoleic acid [23] and ferulic acid [31].

An important role in the management of skin diseases has the assessment of the nutritional status of patients and their education for the preparation and management of a daily food diary, as well as the multidisciplinary

team of doctors, psychologists/psychosomatic [8, 28], nutritionists, dietitians and pharmacists. To these are added the specialists from the food industry, for the research-development of foods for special nutritional states. Preclinical studies and randomized clinical trials are needed to verify the effectiveness of the diet/food for special nutritional conditions in the management of skin diseases. The establishment of the diet for patients with skin diseases is based on multidisciplinary knowledge of sensory qualities, physicochemical properties (biochemical composition of food, water solubility, chemical stability, pH, etc.) and food bioavailability, contraindications for other associated pathologies, or details of food-drug interaction. An essential role in determining the effectiveness of the food/diet is played by determining the dose and duration of treatment with the personalization of patient counselling.

The establishment of the diet for patients with skin diseases is additionally based on multidisciplinary knowledge of sensory qualities, physicochemical properties (biochemical composition of food, water solubility, chemical stability, etc.) and food bioavailability, contraindications in case of other associated pathologies, metabolomics, or details of food-drug interaction [11]. The establishment of dietary therapy should be aimed at preventing possible side effects caused by plant resources, such as *Ginkgo biloba*, vitamin E, usual acid and others [12].

Conclusions

Dietary therapy of skin diseases is a real complementary method that can significantly improve patients' quality of life. For high efficacy, due to the complexity of possible causes, the composition of foods or dietary supplements, as well as possible side effects, diagnosis and dietary therapy in dermatology must be approached multidisciplinary and long-term.

Nutraceuticals are a viable solution for the amelioration or treatment of skin diseases. Due to the fact that they can be certified organic, Halal or Kosher, they can be consumed both by patients with different religions and by people who are followers of a healthy environment.

Conflict of interest

The authors declare no conflict of interest.

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