

Importance of food in the control of inflammation in atopic dermatitis

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Abstract. Patients that suffer from inflammatory diseases need to pay special attention to nutrition. For this reason, it is very important to change the approach of both health professionals and food industry specialists. There must be a close collaboration, starting from research, the development phase of foods for special nutrition states. Our primary objective was to identify foods or potential dietary ingredients, which efficacy in the treatment of atopic dermatitis had been scientifically demonstrated *in vitro*, *in vivo* and clinically. Furthermore, our perspective is presented regarding the research and development of foods for special nutritional states in atopic dermatitis. The PubMed database was analyzed for the period 2018-2020, as well as the European Legislation regarding the appropriate requirements for the composition and knowledge applicable to foods destined for use in special medical purposes. The search criteria were 'chronic dermatitis', 'atopic dermatitis', 'psoriasis', 'alternative treatments', 'natural treatments', 'complementary treatments', 'treatments for chronic dermatitis'. We also looked

for undesirable effects or side effects of the foods included in the research in order to treat atopic dermatitis. The results showed that prebiotics, probiotics and certain plant extracts had a high efficacy in controlling inflammation in atopic dermatitis. The food development research for special nutrition states (atopic dermatitis) involves a multidisciplinary team. We started with the establishment of the general objective and continued with the consultation of the PubMed, EMBASE and other databases, and with the *in vitro*, preclinical and/or clinical determination of the efficacy of new developed foods, that must be protected with patents. The development of foods for special nutrition states represents a solution for improving the quality of life of atopic dermatitis patients.

Introduction

Atopic dermatitis (AD) has a multifactorial pathology (immunological, genetical, environmental factors and skin barrier damage) with specific complex mechanisms (1,2). There are certain foods that can trigger atopy, such as peanut allergy due to the MALT1 gene (3), chicken egg allergy (4), cow's milk or breast milk [due to changes in the sCD14 gene caused by environmental factors in today's society, that include the immune modulators from breast milk (5)] or fish (6). Also, the consumption of processed foods and/or energy drinks (7), antenatal exposure to some heavy metals (Plumb and Chrome) could determine the AD development after 24 months (8). Other substances that can cause AD are: Sodium monoglutamate (9), olive pollen (due to β -1, 3-glucanase rOle e9), allergen produces by *Aspergillus* (due to MnSOD rAsp f6 IgE) (10) or dust mites (11). So far, there are few dermato-endocrinological studies regarding the involvement of adipokines in the AD pathogenesis. Banihani *et al* (12), from Jordan, found that 38.7% of the patients with AD had been associated with some leptin genes that are polymorphic. The study showed that one of them (rs2167270) has the most important role.

Nutrition is one of the most important elements in improving the patients' quality of life in AD. There are preclinical studies that have shown that the systemic immunoregulatory effect of the probiotic bacterium *Lactobacillus pentosus* KF340 (LP340) (present in different fermented foods) was induced by interleukin (IL)-10, produced by Tr1

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Abbreviations: AD, atopic dermatitis; MALT1, Mucosa-associated lymphoid tissue lymphoma translocation protein 1; sCD, soluble form of cluster of differentiation; MnSOD, manganese superoxide dismutase; IL, interleukin; Tr1 cells, type 1 regulatory cells; HACCP, Hazard Analysis of Critical Control Points system; SCFAs, Short-chain fatty acids; Th1, T helper cells; TGF, transforming growth factor; IFN, interferon; RNA, messenger ribonucleic acid; MLN, mesenteric lymph node; GCs, goblet cells; GBA, glucocerebrosidase; Ig, immunoglobulin; MDC, macrophage-derived chemokines; CCL, chemokine ligand; GATA3, transcription factor; ROR γ t, Retinoid-related orphan nuclear receptor γ t

Key words: atopic dermatitis, foods for special nutritional states, inflammation, treatments for chronic dermatitis, complementary treatments

cells (13). Also, *Bifidobacterium adolescentis* and *lactis*, *Lactobacillus sakei*, *acidophilus* and *casei* and Longum are beneficial probiotic bacteria (14,15). In order to suppress the allergic effect of pasteurized cow's milk, Abbring *et al* (16) treated it with alkaline phosphatase and obtained positive preclinical results.

The manufacture of safe food products for human health is performed in compliance with the rules of good hygiene and manufacturing norms (the HACCP principles). In translation, HACCP means: Risk analysis and determination of crucial control points, just like the production recipes specific to each economic agent or of the established/traditional recipes. The Regulation (EU) 218/2016 is available and presents the specific requirements in order to respect the composition and the information applicable to foods intended for particular medical purposes. According to the 4th paragraph, 'The composition of foods intended for special medical purposes may vary greatly depending on, among other things, the specific pathology, disorder or disease for which the diet is designed, the age of the patients and the place where they receive medical care or for the intended use of these products. In particular, foods intended for special medical purposes may be classified by composition into different categories, standard nutritional formula or an adapted nutritional formula, specific to a pathology, disorder or disease, or whether or not they constitute the only food source for the persons whom they are intended' (17).

The efficacy of the active substances (for which there is preclinical/clinical research presented in this paper) and the fact that they have been administered orally are the basis for developing foods to special nutritional states, in our case for AD.

The food industry operators who want to research and develop foods for special nutritional states, in our case for AD, must form multidisciplinary teams that consist of food industry specialists and health professionals. Paragraph 3 of the aforementioned European Regulation, states that 'Foods for special medical purposes are developed in close cooperation with health professionals for the nutrition of patients with pathological disorders, suffering from a disorder or a specific disease or malnutrition due to these diseases which makes it impossible or very difficult to meet the nutritional needs of these patients through the consumption of other foods' (17). According to this paragraph 'For this reason, foods intended for special medical purposes should be used under medical supervision which can be provided with the assistance of other competent persons working in the health field' (17).

Materials and methods

The PubMed database was analyzed for the period 2018-2020. The search criteria were 'chronic dermatitis', 'atopic dermatitis', 'psoriasis' 'alternative treatments', 'natural treatments', 'complementary treatments', 'treatments for dermatitis chronic'. We also looked for undesirable or side effects related to foods, potential food ingredients and the action mechanisms of the analyzed foods. In the period 2018-2020 we identified 461 articles, of which 95 were preclinical researches and 265 clinical trials. Out of all the analyzed articles, only 31 were important for us, in order to achieve our objectives.

In this investigation we have tried to identify and to present foods and potential food ingredients for which there is scientific evidence and we formed a proposal the principles of research and food development for special nutritional states, for atopic dermatitis.

Results

The foods with systemic immunoregulatory effect used preclinically in the treatment of AD were determined. These are summarized in Table I. The foods and substances which efficacy has been clinically determined *in vitro* are presented in Tables II and III.

Considering the multidisciplinary character of the teams (medical, pharmaceutical and food industry) necessary to develop the food for special nutritional states (in our case for AD), we propose the general principles underlying this process as indicated in Fig. 1.

The industrial protection of foodstuffs for special nutrition states is shown in Fig. 2.

Discussion

Preclinical research was performed over a large range of days from 7 to 77 days (Table I). The animal behavior did not change during the research. In these studies, the topical use of some substances (DNFB, DNFB and DEE) (13,15,18,20-24,26), some nutrients (cow milk, red Korean ginseng) (16,21), UV radiations (25) and injections with Apigenin (19) could explain the appearance of skin lesions in AD.

Both *in vivo* and *in vitro* research has demonstrated the efficacy of prebiotics and probiotics [LP340 (13), L-92 (14), *B. adolescentis* (15), Cheongguk-jang (20), Duolac ATP (23), *L. sakei* WIKIM30 (26), Bacterial mixture of lactic acid (27)], plant extracts [*Alnus sibirica* (18), Korean red ginseng (21), Cinamamide (22)] and certain plant resources [β -GdAP (24), CAPS (25), Korean Red Ginseng Extract (28), Strawberry seed extract (tiliroside) (30)] in alleviating the symptoms of atopic dermatitis (erythema, scaling/drying, erosion, edema and itching) (Tables I and II). This is due to the increase of IL-10, IL-12, CD40, CD80 and CD86, T cells spleen regulators, Firmicutes, Chao1 index, colonic SCFAs, Th1, TGF- β , IL-2, IFN- γ , Galectin9 mRNA expression in MLN, GCs and GBA, IL-6 and to the decrease of TGF- β 1, IgE, macrophage-derived chemokines (MDC/CCL22), IL-12 p40, apoptotic cells, B cells, T cells, CD4⁺, CD8⁺, CD19⁺, IL-4, IL-5, IL-13, GATA3 and RoR γ t mRNA expression.

There are meta-analyses that sustain the beneficial anti-inflammatory effects of topical Janus kinase inhibitors in some inflammatory diseases (psoriasis, atopic dermatitis) (31). An other attractive therapy for AD is the topical phosphodiesterase inhibitors that act by reducing the release of proinflammatory cytokines (32).

The efficacy of Korean red ginseng in the treatment of AD has been demonstrated preclinically and clinically. This product determines the growth of: Hydration degree, lipid layers, angiogenesis and neovascularization, epithelization, fibroblast activity, collagen accumulation (21) and IGA (28) (Tables I and II). It also determines the decrease of skin regeneration time, severity of the disease, EASI score,

Table I. Systemic immunoregulatory effect of food in the treatment of AD determined preclinically.

Preclinical determination of the efficacy of the products/preparations							
Product/preparation, dose, mode of administration	Pathology followed	Species/line, sex, age (weeks)	Number animals/ number groups	Period, number of days	Induction mechanism pathology	Main action monitored and demonstrated	Action mechanism of a product/preparation
LP340 ^a , 800 pg/ml, food (13)	AD (13)	Mice/BALB/c (13)	NM ^a (13)	77 (13)	20 μ l of 1.5% DNCB ^a -topical (13)	- IL-10 and IL-12 \uparrow ; - PD-L1 ^a Socs-3 ^a , Ido ^a \uparrow ; - TGF- β 1 ^a \downarrow ; -CD ^a 40, CD80 \downarrow - thickness of ear lobe \downarrow ; - the injuries caused by the DNCB \downarrow (13)	The IL-10-producing Tr1 induced by LP340 are functional: IL-10 \uparrow ; IL-27 \downarrow (13)
<i>B. adolescentis</i> ^a , suspension/0.2 ml (1x10 ⁹ UFC), oral (15)	AD (15)	Mice/C57Bl/6, females/6 weeks (15)	20/4 (15)	35 (15)	0.5% DNCB solution: acetone/olive oil + 0.2% DNCB-topical (15)	- Ear thickness \downarrow ; - Mast \downarrow ; - Spleen regulatory T cells \uparrow ; - Th2 \downarrow ; -IgE seric \downarrow ; - IL-4 \downarrow ; -IL-13 \downarrow ; - chemokines derived from macrophages (CDM/CCL22) \downarrow ; - <i>Firmicutes</i> \uparrow ; - Chao1 index \uparrow ; - Colonial SCFA \uparrow (15).	Metabolism of fructose and mannose, SCFA \uparrow ; IFN- γ \uparrow ; - Regulatory T cells \uparrow ; - Th2 \downarrow ; IL-4 and IL-13 \downarrow (15)
<i>Alnus sibirica</i> , fermented extract/100 mg/kg, 100 μ M/kg, oral (18)	AD (18)	Mice/BALB/c Male/7 weeks (18)	30/6 (18)	28 (18)	20 μ l 1% DNCB and 20 μ l 0.5% DNCB (18)	- Antioxidant activity \uparrow ; - IgE \downarrow ; Th2 \downarrow ; - Th1 \uparrow ; -IL-4, -5, -10, -13 \downarrow ; -TNF- α and IFN- γ \downarrow (18)	Hirsute-nona, Muricar-pon B (18)
Cow's milk pasteurized and improved with ALP ^a , 0.5 ml, oral (16)	Allergy (16)	Mice C3H/HeOuJ/females/3 weeks (16)	48/6 (16)	28 (16)	20 mg chicken egg protein dissolved in 0.5 ml PBS ^a containing 10 μ g CT ^a for 5 days; 0.5 ml raw milk 8 consecutive days (16)	IgE \downarrow ; Th2 \downarrow ; IL-13 \downarrow ; CD103 \uparrow ; CD11b \uparrow ; DC \uparrow ; TGF- β \uparrow (16)	Suppression of allergic effect: IgE \downarrow ; Th2 \downarrow ; IL-13 \downarrow ; CD103 \uparrow ; CD11b \uparrow ; DC \uparrow ; TGF- β \uparrow (16)
Apigenin, 150 mg/kg body, oral (19)	AD (19)	Mice ICR (19)	20/4 (19)	7 (19)	Compound 48/80, 50 μ g injection for induction of scratching behavior (19)	- IL-31 \downarrow ; -IL-31 release in HMC-1 cells; Suppression of scratches behavior (19)	mARN IL-31 \downarrow ; Inhibition of MAPK ^a and phosphorylation NF- κ B ^a (19)

Table I. Continued.

Preclinical determinations of the efficacy of the products/preparations							
The product/preparation, dose, mode of administration	Pathology followed	Species/line, sex, age (weeks)	Number animals/ number groups	Period, number of days	Induction mechanism pathology	Main action monitored and demonstrated	Action mechanism of a product/preparation
Cheongguk-jang ^a , oral (20)	AD (20)	Hairless mice/ males/4 weeks (20)	20/4 (20)	20 (20)	Compound 48/80, for inducing scratching and pruritus behavior, 0.1 ml 0.15% DNCB (prepared with acetone/olive oil in a ratio of 3:1) (20)	- SCORAD ↓; - The thickness of the epidermis ↓; - Deposition of collagen fibers on the skin of mice with AD ↓; - Prevention of mast cell infiltration in the dermis of mice (20)	- IgE ↓; -Th2 ↓; - IL-4 ↓; - IL-31 ↓; - mARN IL-31 ↓; - Inhibition of MAPK ^a and phosphorylation NF-κB ^a (20)
Korean red ginseng ^a (21), capsules, 500 mg RG ^a /capsule (2.5 g/kg body), oral (dissolving RG powder in water) (21)	AD (21)	Rats SD ^a , male, 6 weeks (21)	20/4 (21)	27 (21)	Making two round wounds with a diameter of 2 cm (21)	- Moisture in the skin ↑; - Leather lipids ↑; - Angiogenesis ↑; - Epithelialization ↑; - Very active fibroblasts; - Active neovascularization; - Collagen accumulation ↑; - The regeneration time ↓ (21)	- TGF-β1 ^a ↑; - VEGF ^a ↑; - MMP-1 ↑; - MMP-9 ↑ (21)
Cinamamide (NCT and NCPA) ^a , 50 mg/kg/day, oral (22)	AD (22)	Mice/BALB/c, male, 8 weeks (22)	18/6 (22)	28 (22)	20 ml of DEE ^a , 20 ml 1% DNCB (22)	- Thickness of the epidermis and dermis of the ear ↓; - Mast cell infiltration; - IgE ↓; - IgG2 ↓; -IL-4 ↓; - Weight and size of cervical lymph nodes (22)	- mRNA of Jurkat cells ↓; - mRNA of Th1 and Th2 cytokines ↓ (22)
Duolac ATP ^a , 2x10 ⁶ CFU/200 μl/day, oral (23)	AD (23)	Mice/BALB/c, females, 7-10 weeks mice NC/Nga 4 weeks (23)	18/3 (23)	59 (23)	- DEE ^a , - DNFB ^a (23)	- S.F. ^a - No.; - BMDCs ^a - regulated/immune response: PD-L1 ↑, IL-10 ↑, TGF-β1, IL-12p40 ↓, - Improvement of AD symptoms: • Erythema, scaling/drying, excoriation/erosion, edema and itching ↓; • apoptotic cells ↓; • IgE seric total ↓; - Achieving cell balance T: Th1 ↑, Th2 ↓ and Th17 ↓; - IL-2 ↑, IFN-γ ↑; -Maintaining the balance of T cells: yes (23)	- mARNm of IL-10 ↑; - TGF-β-unchanged; - Intestinal Treg cell population ↑ (23)

Table I. Continued.

Preclinical determinations of the efficacy of the products/preparations							
The product/preparation, dose, mode of administration	Pathology followed	Species/line, sex, age (weeks)	Number Animals/ number groups	Period, number of days	Induction mechanism pathology	Main action monitored and demonstrated	Action mechanism of a product/preparation
β-GdAP ^a SM-2001, oral: 1 mg/kg body ^a - group 1; 10 mg/kg body ^a - group 2; 20 mg/kg body ^a - group 3, oral (24)	AD (24)	Rats SD, male, 6 weeks, mice ddY, male, 6 weeks (24)	60/6 (24)	14 (24)	- COM in ddY mice, and after 7 days 10 μl topically (24)	• Vasodilation ↓; • serum histamine ↓; -effects of bGdAP on allergic itching and contact dermatitis: • inflammation ↓; • scratches behavior ↓; • thickness of the epidermis ↓; • pruritus ↓; - FOXP3* and galectin-9 stimulation: • inflammation ↓; • scratches behavior ↓ (24).	- Th2 ↓ (24)
CAPS ^a , 0.2-1% powder, oral (25)	AD/ Hydration of the skin/ UV (25)	Mice Hairless Hos: HR-1, females, 5 weeks (25)	40/4 (25)	25 (25)	- UV radiation (25)	• scratches behavior ↓ (24). - IL-6 ↓; -MMP-13 ↓; - Moisture in the skin ↑; - IL-10 ↑ (25)	- Non-itemized (25)
<i>L. sakei</i> WIKIM30, CFU, oral (26)	AD (26)	Mice/BALB/c, male, 6 weeks (26)	20/4 (26)	63 (26)	DNCB in acetone/ olive oil (3:1); 0.2% DNCB (26)	- Th2 ↓; - CD4 ⁺ ↓, cell T ↓; CD8 ⁺ ↓, CD19 ⁺ ↓, Cell B ↓; - IL-4, -5 and -13 ↓; - MLN: CD25 ⁺ ↑, Foxp3 ⁺ ↑; - IL-10 ↑ (26)	- Non-itemized (26)
Bacterial mixture of lactic acid ^a (conc. ^a 2%; t 2x10 ⁹ CFU/g in 0.2 ml PBS), with sodium butyrate (conc. 100 mM/0.2 ml in 0.2 ml PBS, oral (27)	AD (27)	Mice/BALB/c, male, 3 weeks rats SD, male, 4-6 Weeks (27)	20/5 (27)	41 (27)	Whey protein; TC (27)	- The thickness of the ears ↓; -GATA3 and the expression Rorγt mRNA ↓; - Galectin9 mRNA expression in MLN ↑; -Th1 ↓; -The quality of the gut microbiota ↑; <i>Firmicutes</i> ↑ (27)	- IL-10 ↑; -Th2 ↓; - <i>Galectin9</i> modulates mast cell degranulation and cell differentiation (27)

^aLP340, *Lactobacillus pentosus* bacteria, present in different fermented foods; NM mentioned; DNCB, 2,4-dinitrochlorobenzene; IL, interleukins; PD-L1, Socs-3 and Ido-inhibitory/tolerogenic genes; TGF-β1, transforming growth factor β1; CD, stimulation proteins; IgE, immunoglobulin E; *B. adalescentis*/B.A., *Bifidobacterium adalescentis*; ALP, alkaline phosphatase; PBS, solution containing phosphate buffered saline; CT, cholera toxin; Cheonggukj, a new product containing soybean fortified with Bacillus amyloliquefaciens SCGB1 (SFBA); RG, Red Ginseng; adm, administration; TGF-β1 and VEGF-genes; Cinnamamides, (E)-3-(4-hydroxyphenyl)-N-phenylethyl acrylamide (NCT) and N-trans-coumaroyltiramine (NCPA); DEE, *Dermatophagoides farinae* extract; Duolac ATP^a-probiotic preparation containing four probiotic strains: *L. casei* CBT LC5 (KCTC12398BP), *L. plantarum* CBT LP3 (KCTC10782BP), *L. rhamnosus* CBT LR5 (KCTC12202BP) and *B. lactis* CBT BL3 (KCTC11904BP); S.F, Side effects; BMDCs, (CD11c + BM), in which BM-bone marrow cells; CD11c, CD11c is a type 1 c transmembrane protein; SD, Sprague-Dawley; DNFB, dinitroforbenzene, 1/10/20 mg/kg body β-glucans derived from *Aureobasi-dium pullulans* SM-2001, according to the adult guide obtained from Glucan Co. (Seoul, Korea), 250 mg/60 kg body weight; COM-promoter of histamine secretion; βGdAP-β-1,3 and β-1,6 glucans obtained from the strain of the black yeast *Aureobasi-dium pullulans*; FOXP3, specific marker; CAPS, Polysaccharide (galactose and arabinose) derived from black currants (*Ribes nigrum* L.), *Lactobacillus sakei*; WIKIM30, Lactic acid bacteria mixture-*Lactobacillus sakei*; *Lactobacillus rhamnosus*, *Lactobacillus plantarum* and *Bifidobacterium lactis*; conc, concentration; ↑, increase; ↓, decrease.

Table II. Systemic immunoregulatory effect of food clinically determined in treating AD.

Active substance/dose	Main action monitored and demonstrated	Action mechanism of the drug/subst. Assets	Side effects
L-92 ^a /20 mg (14)	-The median value of SCORAD ↓; -Median value of drug scores ↓; -IDQOL ^a ↑ (14).	-Total IgE ^a ↓; -Th2 ↓; -TARC ^a ↓; -Lecithinase (-) Clostridium ↓; -Enterobacteriaceae ↓ (14).	No (14)
Korean Red Ginseng Extract (28)	-Severity of the disease ↓; -EASI score ^a ↓; -Transepidermal water loss ↓; -VAS ^a for sleep disorder and itching ↓; -The amount of topical agents used ↓; -IGA ^a ↑ (28).	-IgE ↓; -TNF-α ↓; -IFN-γ ↓; -IL-31 ↓; -mARN TNF-α ↓ (28).	Yes (28)

^aL-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 Analog Scale; IGA, Investigator global assessment; ↑, increase; ↓, decrease.

Table III. Alternative foods/treatments determined *in vitro* with systemic immunoregulatory effect in treating AD.

Active substance	Main action monitored and demonstrated
<i>Alnus sibirica</i> , fermented (18,29), fermentation	- <i>In vitro</i> cytokine regulation; - Missing cytotoxicity (on RBL-2H3 cells); -IL-12 ↑; -IFN-γ and IL-4 ↓ (on RAW 264.7 cell lines) (18,29). - Treg differentiation: proliferation of CD4 ⁺ T ↑, Foxp3 +/Tregs ↑, IL-10 ↑; -IFN-γ ↑, IL-4 ↓ (23). - Ceramide synthesis in the stratum corneum ↑, with the exception of ceramide [EOS], [API]; - Skin barrier function and moisture retention ↑; -GCS and GBA ↑; SPT2 and CerS3, not influenced (30). - Modulation of DC and T cells: • TNF-α ↑, IL-6 ↑, IL-12p70 ↑, IL-10 ↑; • CD40 ↑, CD69 ↑, CD80 ↑, CD86 ↑ și MHCII ; • PD-L1 ↑ and CD103 ↑;
Duolac ATP ^a , x10 ⁶ CFU/ 200 μl/day (23)	• D4 ⁺ ↑, CD25 ⁺ ↑, Foxp3 ⁺ ↑, Tregs ↑; -Modulation of T cell immune responses: • Th2 ↓, IL-4 ↓, IL-10 ↑;
Strawberry seed extract (tiliroside), 1.0-3.0 μg/ml (30)	• Improvement of specific lesions AD; • IgE ↓ (26).
<i>L. sakei</i> WIKIM30, 2x10 ⁹ CFU, oral (26)	

^aDuolac ATP^a-probiotic preparation containing four strains of probiotics: *L. casei* CBT LC5 (KCTC12398BP), *L. plantarium* CBT LP3 (KCTC10782BP), *L. rhamnosus* CBT LR5 (KCTC12202BP) and *B. lactis* CBT BL3 (KCTC11904BP); ↑, increase; ↓, decrease.

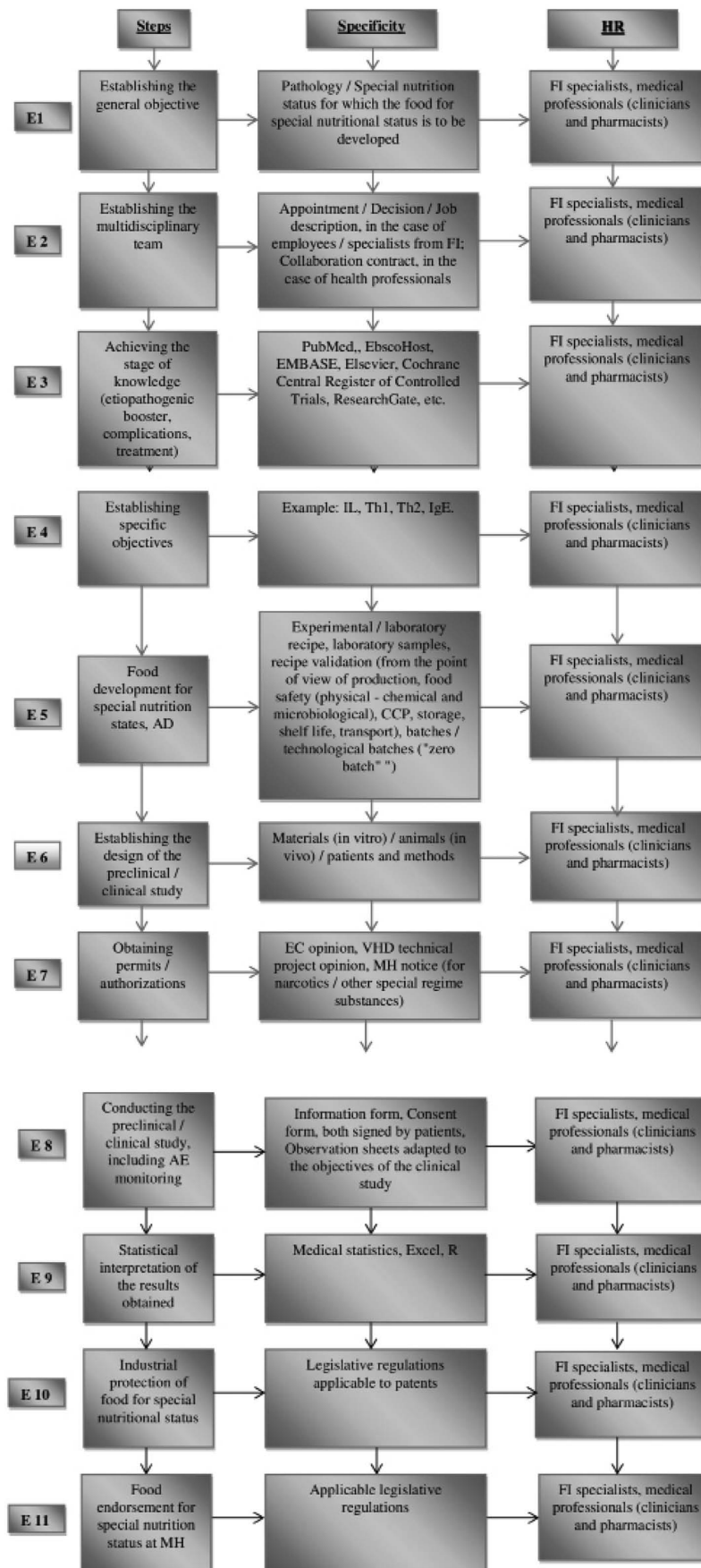
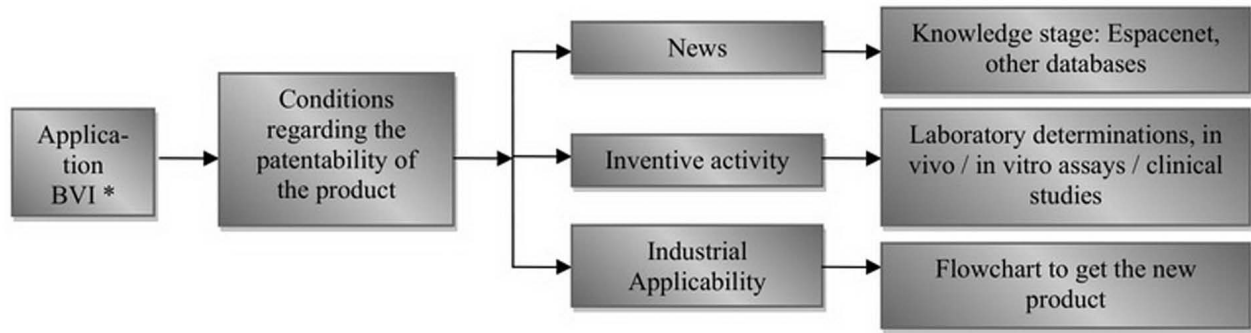


Figure 1. Food development for special nutrition states. General principles. E, stage in the research process - development of foods for special nutrition states, *in vitro*/preclinical/clinical evaluation and their approval to the MH; HR, human resources; FI, food industry; IL, interleukins; Th, T helper cells; IgE, immunoglobulin E; CCP, critical control point (it is essential for food safety. It is the stage in which a control measure can be used to prevent or eliminate a food safety hazard or to reduce it to an acceptable level); AD, atopic dermatitis; EC, Ethics Committee; VHD, Veterinary Health Department; MH, Ministry of Health; R, program of medical statistics; AE, adverse events.



*BVI-Patent of invention

Figure 2. Industrial protection of food stuffs for special nutrition states. PI, patent of invention.

transepidermal water loss, visual analog scale, SCORAD (that quantified also the itching and lack of sleep) and the number of topical agents used (28).

From a legislative point of view, we consider that the European authorities (Commissions, Medicine Agency and Food Safety Authority) and national authorities (the Ministry of Health), should issue a common guide for all the countries in the EU. This guide must provide the principles of the development of food for special nutritional states, such as: The etiopathogenic booster, the diagnostic problems, the diagnosis of complications, the treatment (hygienic-dietary regimens, drug treatment). It should complete the legislative regulations in order to obtain the Notice of the Ethics Commission for conducting preclinical/clinical studies and also for foods for special nutritional states. This notice is not only for drugs and/or dietary supplements but also for the nutriviigilance system that identifies and monitors the side effects caused by the new foods for special nutritional states, similar to the existing pharmacovigilance system.

The development of foods for special medical purposes requires multidisciplinary knowledge and multiple resources. Out of all the resources, time is the most expensive one because the determination of the efficacy of these products takes a lot of time.

To develop the foods for special nutritional states we need to know the etiopathogeny of the disease, the symptomatology and the pharmacological principles (Fig. 1).

The top management of food factories that want to manufacture food for special nutritional conditions, must have multidisciplinary teams, specialized in research and development of these products, or collaborate with health professionals. The principles proposed in Fig. 1 are also valid for the development of food supplements.

Industrial protection (obtaining the invention patent) is a long-term process. It is based on the verification of the stage of knowledge (including patents filed worldwide), physico-chemical and preclinical/clinical analyzes. Also, it is necessary to know the advantages and disadvantages of the new developed food for special nutritional status in comparison with others existing patents (Fig. 2).

In conclusion, the development of foods for special nutritional states represents a solution for improving the quality of life of atopic dermatitis patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MR contributed in the conception and design of the study, analysis and interpretation of the data, manuscript drafting and critical revision of the manuscript for important intellectual content. GMI was responsible for the analysis and interpretation of the data, manuscript drafting and design, and critical revision of the manuscript for important intellectual content. IMM contributed in the conception and design of the study, data acquisition, analysis and interpretation of the data, manuscript drafting and design, and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests and they have no financial relationships to disclose.

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