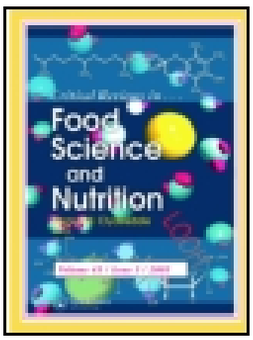

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REVIEW

Nutrition and immune system: from the Mediterranean diet to dietary supplementary through the microbiota

Luigi Barrea[a,b]*, Giovanna Muscogiuri[a,b]*, Evelyn Frias-Toral[c]*, Daniela Laudisio[a,b], Gabriella Pugliese[a,b], Bianca Castellucci[a,b], Eloisa Garcia-Velasquez[d], Silvia Savastano[a,b], and Annamaria Colao[a,b,e]

[a]Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, Naples, Italy; [b]Centro Italiano per la cura e il Benessere del paziente con Obesità (C.I.B.O), Department of Clinical Medicine and Surgery, Endocrinology Unit, University Medical School of Naples, Naples, Italy; [c]Research Committee, SOLCA Guayaquil, Guayaquil, Ecuador; [d]Clinical Nutrition Service, San Francisco Clinic Hospital, Guayaquil, Ecuador; [e]Cattedra Unesco "Educazione alla salute e allo sviluppo sostenibile," University Federico II, Naples, Italy

ABSTRACT

The interaction between nutrition and the immune system is very complex. In particular, at every stage of the immune response, specific micronutrients, including vitamins and minerals play a key role and often synergistic, and the deficiency of only one essential nutrient may impair immunity. An individual's overall nutrition status and pattern of dietary intake (comprised of nutrients and non-nutritive bioactive compounds and food) and any supplementation with nutraceuticals including vitamins and minerals, can influence positively or negatively the function of the immune system. This influence can occur at various levels from the innate immune system and adaptive immune system to the microbiome. Although there are conflicting evidence, the current results point out that dietary supplementation with some nutrients such as vitamin D and zinc may modulate immune function. An update on the complex relationship between nutrition, diet, and the immune system through gut microbiota is the aim of this current review. Indeed, we will provide the overview of the link among immune function, nutrition and gut microbiota, paying particular attention at the effect of the Mediterranean diet on the immune system, and finally we will speculate the possible role of the main one functional supplements on immune function.

KEYWORDS

Dietary supplements; immune system; Mediterranean diet; microbiota; nutrition; nutritionist

Introduction

Our environment contains a wide range of pathogenic microbes and toxic substances with an extensive selection of pathogenic mechanisms making the immune system critical for survival (Childs, Calder, and Miles 2019). Our immune response is continuously working to prevent attacks from the outside world by acting, answering, and recognizing antigens. It has progressed through time to protect the host from microbes that are themselves constantly evolving (Chaplin 2010). These cells may be divided into those of the innate and the adaptive immune response. Both responses usually act together, making synergy between them essential.

Overview of the immune system

The first line of defense is the innate immune response to invading microorganisms and pathogens. Cells of the innate immune response include all aspects of the host immune defense mechanisms such as macrophages, monocytes, neutrophils, dendritic cells (DCs), mast cells, eosinophils, and others (Kumagai and Akira 2010). An overview of the immune system is shown in Figure 1.

They are essentials for the common bacterial infection control, and it does not increase with repeated exposure to pathogens. Adaptive immunity includes immunological memory; these responses are also known as acquired immune responses. They begin when an immature DC ingests a pathogen. They are generated by clonal selection of lymphocytes, on the antigen-specific receptors expressed on the surfaces of T- and B-lymphocyte, and it manifests specificity for its target antigens. The T cells are divided into cytotoxic T (cluster of differentiation, CD 8 receptor) and T-helper (Th) cells. Other lymphocytes are the B cells, responsible for antibody or immunoglobulin (Ig) production, and each one has a specialized role. There are five classes of Ig (IgM, IgD, IgG, IgA, and IgE) and among them, IgA has a role in neutralizing food antigens and preventing food allergies. T and B cells can recognize the antigen and respond rapidly since they can become memory

CONTACT Luigi Barrea luigi.barrea@unina.it Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, 80131 Naples, Italy.
*These authors have equal contribution and should be considered as co-first authors.
*Present address: Clinical Research Associate Professor for Palliative Care Residency from Universidad Católica Santiago de Guayaquil, Av. Pdte. Carlos Julio Arosemena Tola, Guayaquil 090615, Ecuador.

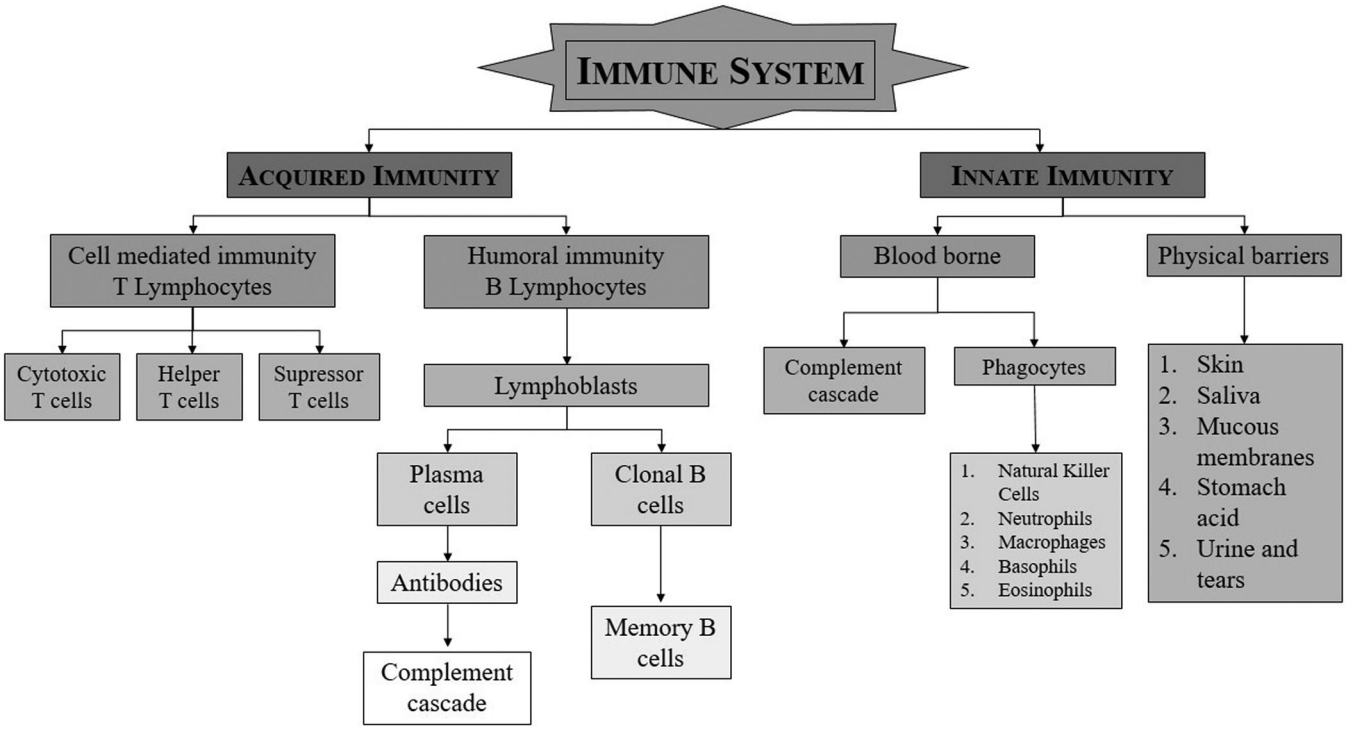

Figure 1. A brief overview of the immune system.

cells (Childs, Calder, and Miles 2019). Both systems also protect against native cells like the cancerous or precancerous cells. Communication is needed to coordinate the innate and adaptive systems and it is dependent on the cell-cell interactions as well as on the production of chemical messengers, including tumor necrosis factor (TNF) and cytokines such as interleukins (ILs) and interferon (IFN).

The gut-associated lymphoid tissue (GALT) has the majority of immune cells within the human body. DC and microfold cells (or M cells) are in the gut content, while plasma B cells within the lamina propria produce IgA (Childs, Calder, and Miles 2019). Gut Barrier defects or leakages of the mucous membranes are critical for the pathogenesis of many diseases, including respiratory, gastrointestinal, and urinary tract infections as a consequence of the microbial flora (Cunningham-Rundles, McNeeley, and Moon 2005). Gut microbiota diversity plays a crucial role in physiology and the development of chronic diseases, due to its ability to stimulate immunity as it can regulate inflammatory, metabolic, and infectious diseases. Prebiotics, probiotics, and symbiotics have been shown to restore innate and adaptive immunity, and reconstructing alterations of gut microbiota contributes to immune homeostasis (Soldati et al. 2018). The immune response has to distinguish itself from non-self-invading pathogens to avoid unleashing these destructive mechanisms against the host's tissues, and it must evade responses that eliminate beneficial, commensal microbes (Chaplin 2010).

Inflammation is the result of the immune response activities that protect the host from infections; it is an outcome of effective immune activities. The inflammatory response is beneficial as an acute, transient reaction to damaging conditions. There are concerns with chronic, systematic, low-grade inflammation with dietary and lifestyle changes by constantly raising inflammatory markers in the systemic circulation (Calder et al. 2011).

The immune system needs adequate and appropriate nutrition to function optimally. Prolonged undernutrition and micronutrient deficiency affect cytokine response and immune cell trafficking. The combination of chronic inflammation and malnutrition impairs the immune response. However, not only undernutrition is a concern, patients with obesity (excess storage of fat) have shown chronic low-grade inflammation with higher concentrations of inflammatory markers in the systemic circulation. The fatty acid composition of immune cells affects the regulation of the immune response. It is common to see altered T-lymphocyte and increased TNF-α production in this population (Cunningham-Rundles, McNeeley, and Moon 2005).

Role of nutrition in immune function

Nutrition and food are the major exogenous factor that plays an essential role in the immune defense response; it can also be affected by endogenous sources like body stores as fat and muscle composition. For example, Calder et al. described how a low postprandial grade systemic inflammation, because of our meals, can contain oxidized components that initiate oxidative stress and/or inflammatory responses upon absorption. After meals, there is an elevation in the concentrations of inflammatory mediators in the bloodstream; this mechanism can be exaggerated in patients with type 2 diabetic and obesity (Calder et al. 2011).

Adequate nutrition can reduce or delay immune-mediated chronic diseases (Childs, Calder, and Miles 2019). Furthermore, gut microbiota can also mediate the immunological effect. Chandra published that in healthy adults, the

major determinants of immune competence are lifestyle-related factors such as diet and sleeping habits, stress, sedentary lifestyle, exercise, traveling, pollution, smoking, alcohol, and substance abuse (Chandra 1997). A recent review paper highlighted that an individual's nutritional status can impact the functioning of the immune system, intestinal mucous membranes, the microbiome, and both the innate and the adaptive immune system (Venter et al. 2020). Notably, the incidence of immune-mediated diseases is elevated in Westernized countries. Healthy components of a diet, like whole grains, vegetables and fruits, and fish like a source of omega-3 fatty acids, are all associated with lower inflammation (Calder et al. 2011). The polyunsaturated fatty acids (PUFAs) influence on the immune system through the diet specially focused on omega-3 PUFAs α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Gutierrez, Svahn, and Johansson 2019). Fatty acids like omega-3 are part of the cellular membrane that regulates membrane fluidity or complicated assembly. Xiaoxi et al. did an extensive review of the literature and mentioned that the immune cells are particularly sensitive to changes and more susceptible to lipid peroxidation because they contain a high percentage of PUFAs in their plasma membranes (Li et al. 2019). Fatty acids also have an impact on macrophage function like the production and secretion of cytokines and chemokines, the capacity of phagocytosis, and the polarization into classically or activated macrophages (Gutierrez, Svahn, and Johansson 2019). There are also anti-inflammatory properties like decreasing the secretion of IL-1β, TNF-α, and IL-6.

Undernutrition of macronutrients and selected micronutrients can lead to a very significant immunodeficiency with clinical repercussions. It can cause impairment of cell-mediated immunity, phagocyte function, complement system, secretory IgA antibody concentrations, and cytokine production. As a result, the immune system lost the components needed to initiate an effective response. This dietary restriction decreases leukocyte exudation into local inflammatory sites and the production of the chemokine macrophage inflammatory protein.

The effects of micronutrients in the immune system have been well described. The first line of defense acts in the external and internal surfaces of the body and these require to be well structure to function correctly, the maintenance of structural and functional integrity of mucosal cells in innate barriers are made by vitamin A, C, D, E, B_6, B_{12}, folate, iron, zinc. The consequences of its deficiency depend on the grade of the severity and the age of the subject. Iron is essential for the differentiation and growth of epithelial tissue. Vitamin A and zinc are indispensable for the structural and functional integrity of skin and mucosal cells. A lack of vitamin A can also impair T and B cell movements in the intestine. Zinc is a fundamental cofactor for the activity of many enzymes, such as the thymic hormone. Vitamin C is necessary to promote collagen synthesis in epithelial tissue (Gombart, Pierre, and Maggini 2020), and it is an effective antioxidant contributing to the maintenance of the redox integrity of cells and protection against reactive oxygen species (ROS) generated during the respiratory burst and inflammatory responses. Vitamin D is involved in cell proliferation and enhances innate immunity by increasing the differentiation of monocytes to macrophages. Its deficiency can increase the risk of infection and autoimmune diseases such as multiple sclerosis and diabetes. The deficiency of folate causes a reduced immune response and resistance to infections, fewer circulating lymphocytes, decreased proliferation; an increased $CD4^+/CD8^+$ ratio, diminished delayed-type hypersensitivity, and natural killer (NK) cell activity, and debilitated Th1 response (Maggini, Pierre, and Calder 2018).

Immune function may improve by restoring deficient micronutrients to proper levels, thereby decreasing rates of infection and supporting faster recovery when infected. An adequate dietary regimen can maintain the equilibrium between the inflammatory and the anti-inflammatory cascade. It must be clear that for some micronutrients, excessive intake can also be associated with impaired immune responses. Micronutrients with the strongest level of evidence are vitamins C (Bozonet et al. 2015; Carr and Maggini 2017; Hemila and Chalker 2019; Huijskens et al. 2014; Maggini, Pierre, and Calder 2018; Schwager et al. 2015), vitamin D (Autier et al. 2017; Bergman et al. 2013; Charan et al. 2012; Martineau et al., 2017; Rejnmark et al. 2017) and zinc (Bonaventura et al. 2015; Gibbons 1977; Maywald, Wessels, and Rink 2017; Sandstrom et al. 1994) for immune support. A schematic representation is shown in Figure 2.

Obesity, a worldwide epidemic, is a significant expansion of adipose tissue mass with changes in body composition. Patients with increased abdominal fat mass are associated with elevated inflammatory cytokines, adhesion molecules, and prothrombotic molecules (Sypniewska 2007). In these patients, systemic concentrations of pro-inflammatory mediators are higher in subjects with obesity (body mass index [BMI] 30.0 kg/m^2) than in normal-weight individuals. Serum or plasma concentrations of TNF-α or IL-6 in healthy adults is lower than in those with higher BMI. Obesity is considered a determinant of the postprandial inflammatory response. The elevated postprandial inflammatory response is reversible upon losing weight (Thomas and Apovian 2017). In vitro studies have shown that mature adipocytes express inflammatory factors. The variation in concentrations of most mediators among non-obese or individuals with obesity is at least 10-fold (Calder et al. 2011). Oxidative damage can compromise the integrity of immune cell membranes, altering membrane fluidity and transmission of signals both within and between different immune cells. A major risk factor for obesity is the western diet, that it is characterized by a high content of sugar, trans fatty acid, and saturated fat acid (SFA). It is known that only long-term consistent dietary patterns and lifestyle changes can benefit human health or provoke inflammation and increased oxidative stress if an unhealthy diet, which will subsequently lead to chronic disease (Thomas and Apovian 2017). For example, there was a significant modification in the expression of inflammatory genes in the subcutaneous adipose tissue of women with obesity that lost weight with a hypo-energetic diet; it is also seen in post-bariatric surgery

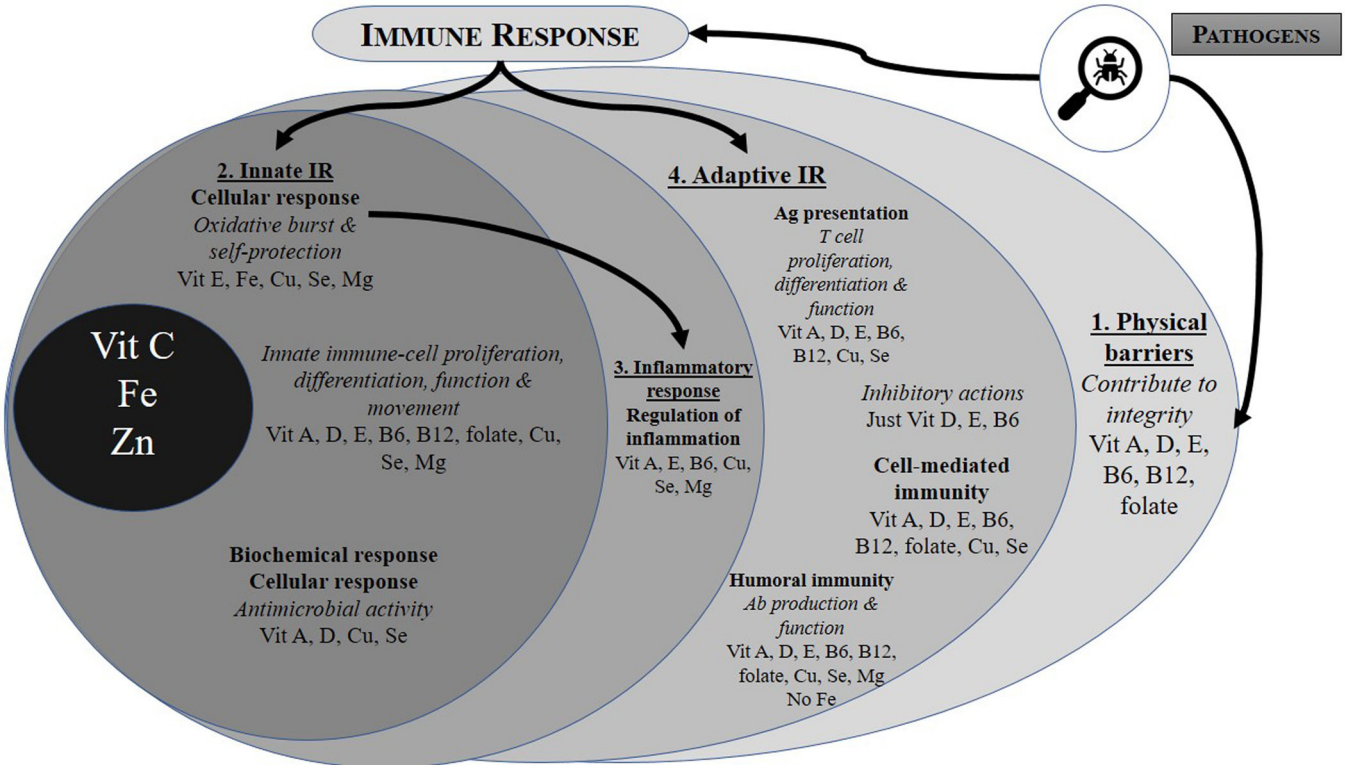

Figure 2. The micronutrients vitamin C, Fe, Zn have essential roles at every stage of the different components of the protection mechanisms against pathogens and are present in almost all of them (core of the figure). Ab, antibody; Ag, antigen; Cu, copper; Fe, iron; IR, immune response; Mg, magnesium; Se, selenium; Vit, vitamin; Zn, zinc.

and its associate to macrophage function (Thomas and Apovian 2017).

The crucial relationship between immune function and nutrition starts in the prenatal stage, in critical periods of gestation and neonatal maturation and during weaning that will affect the adaptive antibody and cellular immune response. Passive immunity is when maternal antibodies, the antigen-specific Ig are transmitted via the placenta before birth, and in through maternal colostrum and milk after birth (Niewiesk 2014). The primary Ig in human maternal milk is IgA, which can not be found in commercial infant formulas. Breast milk contains its unique microbiota, rich in bifidogenic oligosaccharides, and can also stimulate maturation of the GALT.

Nutrients deficiencies alone in a malnourished child can also cause specific immune deficiencies and have long-term consequences during the development and can cause disease in the future adult. For example, a copper deficiency is associated with neutropenia, anemia, and reduced IL-2 response (Percival 1998).

The protein caloric malnutrition affects more directly the cellular immune system. Primary malnutrition leads to atrophy of the lymphoid organs, T-lymphocyte deficiency, and increased susceptibility to pathogens, reactivation of viral infections, and development of opportunistic infections (Cunningham-Rundles, McNeeley, and Moon 2005). Thymic atrophy caused by protein caloric malnutrition is associated with hormonal imbalance, loss of leptin, an increase in circulating cortisol levels. It is associated with micronutrient deficiencies such as zinc, magnesium, selenium, copper, iron, vitamin A deficiencies (Cunningham-Rundles, McNeeley, and Moon 2005). It can lead to increased susceptibility to infections and higher morbidity because oxidative stress is worsened in infection if micronutrients are deficient. There are direct relationships between nutrition deficiencies of macro and/or micronutrients with a reduced immune response (Gombart, Pierre, and Maggini 2020; Maggini, Pierre, and Calder 2018; Venter et al. 2020). However, there is greater importance in whether specific nutrients interventions, addressing dosage and combinations, can further enhance immune function in sub-clinical situations or prevent specific immune-related chronic diseases from improving human health (Gombart, Pierre, and Maggini 2020; Maggini, Pierre, and Calder 2018; Venter et al. 2020).

The interaction between nutrition and the immune system is very complex. An individual's overall nutrition status and pattern of dietary intake (comprised of nutrients and non-nutritive bioactive compounds and food) and any supplementation with nutraceuticals including vitamins and minerals, can influence positively or negatively on the functioning of the immune system. This influence can occur at various levels: innate immune system and the adaptive immune system until the microbiome. This review aims to provide an overview of the complex relationship between the immune system, nutrition, diet, and microbiota.

Microbiota influence on diet

The human intestine hosts tens of trillions of microorganisms, which belong to about 300–1000 different species of

bacteria and contain 3 million genes, therefore about 100 times the human genome (Caballero and Pamer 2015). The most represented Phyla are Firmicutes (60%–80%) which include the genera Ruminococcus, Clostridium, Lactobacillus, and Enterococcus; the Bacteroidetes (20%–30%) which include Bacteroides, Prevotella and Xylanibacter; Actinobacteria (<10%) which include Bifidobacterium; Proteobacteria (<1%) which include the genera Escherichia and Enterobacteriaceae (Munoz-Garach, Diaz-Perdigones, and Tinahones 2016).

There is a symbiotic relationship between the microbiota and the host-human: the latter provides the microbes with nutrients and protection while the bacteria guarantee the production of certain vitamins, protection from colonization by pathogens, and the ability to ferment some indigestible carbohydrates (Gill et al. 2006).

The composition of gut microbiota is influenced by both genetic and environmental factors such as birth, natural or cesarean, breastfeeding, sex, age, growth and aging, physical activity, concomitant diseases, and drugs, but above all the diet that represents the factor of greatest impact (Quigley 2017). The various components of the diet may have a different effect on gut microbiota: fiber and carbohydrates are the principal carbon and energy source for colonic microorganism, are fermented by microorganisms with the production of beneficial metabolites such as short-chain fatty acids (SCFAs). These fatty acids lead to changes in the composition of the microbiota as an increase in Bifidobacteria, Bacteroidetes and Akkermansia muciniphila with positive effects enhancing intestinal barrier integrity, motility, insulin sensitivity, and satiety, improving lipid metabolism and decreasing inflammation (Sandhu et al. 2017; Slavin 2013; Sonnenburg and Backhed 2016).

SFA indirectly modulate the microbiota through the metabolism of bile acids determine an increase in Firmicutes, Proteobacteria, and Bilophila spp. and a reduction in Bacteroidetes and Bifidobacterium spp. associated with an increase in endotoxemia, adiposity and insulin resistance (Sandhu et al. 2017; Turnbaugh et al. 2008; Zhan 1989). Moreover, unsaturated fats act on bile acid secretion and composition, resulting in an increase in Bifidobacterium, Lactobacillus, and Akkermansia spp. with a decrease of inflammation and adiposity (Sandhu et al. 2017; Turnbaugh et al. 2008; Zhan 1989).

Proteins are the main source of essential nitrogen for carbohydrate fermentation; a protein-rich diet has been associated with an increase in Bacteroidetes and a decrease in Bifidobacterium spp., such as with a reduction in weight (Conlon and Bird 2014; Sandhu et al. 2017).

Finally, polyphenols represent an energy substrate for some beneficial bacteria and inhibit the growth of some pathogenic strains. Polyphenols consumption is associated with an increase in Bacteroidetes, Lactobacillus, Bifidobacterium, and Akkermansia spp., with a decrease in Clostridium spp. It is related with an improvement in the lipid profile, blood pressure, blood sugar, and anthropometric parameters such as BMI and waist circumference (Cardona et al. 2013; Cross and Klesius 1989; Ozdal et al. 2016).

In particular, regarding the effect of a moderate intake of red wine polyphenols on gut microbiota, it was observed that the daily consumption of red wine polyphenols for 4 weeks significantly increased the number of Enterococcus, Prevotella, Bacteroides, Bifidobacterium, Bacteroides compared with baseline, as well as decreased significantly blood pressure, triglyceride, total cholesterol, high-density lipoprotein (HDL) and C-reactive protein (CRP) concentrations, suggesting that the positive metabolic effect of the polyphenols contained in red wine could be mediated by changes in the composition of the microbiota (Queipo-Ortuno et al. 2012).

Recent epidemiological and intervention studies have suggested that alterations in the composition of the microbiota may result in an increased risk of several chronic diseases including obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, asthma, eczema, depression, colon cancer and inflammatory bowel disease (Akhmedov and Gaus 2019; Kahrstrom, Pariente, and Weiss 2016; Lucas, Barnich, and Nguyen 2017; Muscogiuri et al. 2018). In particular, the microbiota associated with obesity seems to involve an alteration of the carbohydrate and lipid metabolism, of the extraction of energy from food, of the central mechanisms of appetite and reward, an increase in the deposition of body fat and systemic inflammation, and it is characterized by an increase in the Firmicutes/Bacteroidetes ratio (Torres-Fuentes et al. 2017).

Since the different types of diet play a significant role in shaping the microbiome, with experiments showing that dietary alterations can induce large, temporary microbial shifts within 24 hours (Singh et al. 2017), it is important to understand how specific dietary patterns can modify the microbiota. The Western pattern diet is characterized by high intakes of red or processed meat, prepackaged foods, butter, sweets, fried foods, high-fat dairy products, eggs, refined grains, potatoes and high-sugar drinks. A study conducted on mice fed on a Western pattern diet or a diet low in fat and high in fiber was observed that those who had followed a Western pattern diet had a reduction in Bacteroidetes, a proportional increase in Firmicutes, with a prevalence of the single class of Mollicutes and an overall reduction in bacterial diversity (Turnbaugh et al. 2008). Probably the bacteria that made up the microbiota after a Western pattern diet were selected because they had a competitive advantage in processing simple sugars. Furthermore, by comparing the fecal microbiota of European children (EU) with that of children from an African village in Burkina Faso (BF), where the diet, rich in fiber, is similar to that of the first human settlements at the time of the birth of agriculture and consists mainly of cereals such as millet, legumes, and vegetables, using the sequencing of rRNA 16S significant differences were found between the two groups (De Filippo et al. 2010). Of interest, BF compared to EU children showed significant enrichment of Bacteroidetes and depletion in Firmicutes ($p < 0.001$), with an abundance of

bacteria of the genus Prevotella and Xylanibacter, known to contain a set of bacterial genes for the hydrolysis of the cellulose and xylan, completely deficient in EU children. Therefore, the composition of the microbiota of BF children could be co-evolved with their diet rich in polysaccharides, allowing them to maximize the energy intake from the fibers and also protecting them from inflammation and noninfectious colon diseases.

About Mediterranean diet (MD), a dietary pattern characterized by the consumption of cereals preferably as whole grains, legumes, nuts, vegetables, and fruits, in high amount and frequency, several studies have shown that the consumption of foods included in the typical MD determines changes in the composition of the intestinal microbiota leading to an increase in beneficial bacteria such as Lactobacillus, Bifidobacterium, and Prevotella, and a reduction in pathogenic bacteria such as Clostridium, also improving obesity, lipid profile, and inflammation (Del Chierico et al. 2014; Lopez-Legarrea et al. 2014). De Filippis et al. investigated the potential effects of the MD including omnivore, vegetarian and vegan subjects and detected significant associations between degree of adherence to the MD and increased levels of fecal SCFAs, which are considered anti-inflammatory and important for the maintenance of the mucosal barrier, Prevotella bacteria and other Firmicutes (De Filippis et al. 2016). At the same time, low adherence to the MD was associated with elevated urinary trimethylamine N-oxide (TMAO), which is related to increased cardiovascular risk (Barrea, Annunziata, et al. 2018; Barrea, Annunziata, et al. 2019; Barrea, Muscogiuri, Annunziata, Laudisio, de Alteriis, et al. 2019; De Filippis et al. 2016). Due to the spread of celiac disease, the gluten-free diet (GFD) is often practiced, with obvious consequences on the composition of the intestinal microbiota. In a preliminary study on ten healthy subjects, the effects of a GFD over 1 month on the composition of the gut microbiota were analyzed. A reduction of Bifidobacterium, Clostridium, and Faecalibacterium were observed while Enterobacteriaceae and Escherichia coli counts increased after the diet. Therefore, the GFD induce a reduction in beneficial gut bacteria constituting an environmental variable to be considered in treated celiac disease patients for its possible implications on gut health (De Palma et al. 2009).

About vegan and vegetarian diets, the data presented so far in the literature are limited: examining fecal samples of vegetarians (n = 144), vegans (n = 105) and an equal number of omnivorous, total counts of Bacteroides spp., Bifidobacterium spp., Escherichia coli and Enterobacteriaceae spp. were significantly lower in vegan and vegetarian samples than in controls, suggesting that maintaining a strict vegan or vegetarian diet results in a significant shift in the microbiota composition (Zimmer et al. 2012). It would also seem that a vegan diet can improve the metabolic profile by probably acting on the composition of the microbiota. Indeed, in a small study conducted on 6 obese subjects with diabetes and/or hypertension who followed a vegan diet for one month, improved blood glucose levels, triglycerides, total cholesterol, low-density lipoprotein (LDL)-cholesterol, glycated hemoglobin (HbA1c) and reduced body weight were found, as well as a reduced abundance of Firmicutes and an increased abundance of Bacteroidetes, contrasting that alteration of the Firmicutes/Bacteroidetes ratio typical of obesity (Kim et al. 2013).

The impact of microbiota composition on the immune system

The close relationship between diet, microbiota, immunity, and health have been identified for several pathologies: inflammatory bowel diseases (Saman, Coetzee, and Opie 1988), autoimmune diseases like arthritis, multiple sclerosis and type 1 diabetes (Vieira, Pagovich, and Kriegel 2014), NAFLD (Chassaing, Etienne-Mesmin, and Gewirtz 2014) and metabolic syndrome (Santos-Marcos, Perez-Jimenez, and Camargo 2019) suggesting both a link in pathogenesis and a therapeutic chance. One way in which microbiota can influence host health is by modulating maturation, development, and functions of both innate and adaptive immune system and maintaining immune tolerance (Belkaid and Harrison 2017; Rooks and Garrett 2016). Studies in germ-free (GF) animals have demonstrated that the gut microbiome is essential for immune cell recruitment and differentiation as well as for the predisposition to autoimmune diseases. In particular, GF animals exhibit impaired immune development, characterized by immature GALT, decreased numbers of intestinal lymphocytes and diminished levels of antimicrobial peptides and IgA, all of which is reversed upon colonization with commensal bacteria (Chinen and Rudensky 2012). In contrast, GF mice exhibited resistance to experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, but disease susceptibility was restored upon colonization with microbiota (Lee et al. 2011).

The interaction between gut microbiota and the immune system is bidirectional, in fact in addition to providing important energy sources for the intestinal epithelium, the metabolites produced by intestinal microorganisms promote intestinal epithelial cells (IECs) homeostasis, while the IECS, in turn, can secrete and respond to various cytokines and chemokines and express molecules interacting with lymphocytes (Kabat, Srinivasan, and Maloy 2014), mucins, and antimicrobial peptides. Although the precise mechanism by which the intestinal microbiota modifies the immune response is only partially known, it would seem that the mechanisms most involved are the signaling pathway of the G-protein-coupled receptors (GPCRs) and epigenetic mechanisms. About the latter, for example, some microbial-derived SCFAs increase acetylation of histone H3 at the promoter of the gene encoding the forkhead transcription factor (FOXP3) and inhibit histone deacetylases 6 and 9, which lead to differentiation of colonic regulatory T cells and an anti-inflammatory effect (Tilg and Moschen 2015). Regarding the influence of the intestinal microbiota on innate immunity, the microorganisms produce pathogen associated molecular patterns (PAMP), such as lipopolysaccharide (LPS) and metabolites as SCFAs with different

effects (Tilg and Moschen 2015). For example, LPS is recognized by the IECs through toll-like receptors (TLRs) 4 and induces secretion of antimicrobial peptide - RegIIIγ that protects the intestine from the colonization of pathogenic bacteria in addition to exerting modulatory functions on chemotaxis, TLR signaling and IECs proliferation (Brandl et al. 2008; Miyaoka et al. 2004). Moreover, microbial colonization of GF mice triggers epithelial expression of RegIIIγ, which would seem to exert its antimicrobial activity directly binding bacterial targets via interactions with peptidoglycan carbohydrate (Ideishi et al. 1990).

SCFAs such as acetate, butyrate, and propionate, which are generated by microbiota-mediated processing of dietary fiber and non-digestible carbohydrates, are indispensable messengers in the crosstalk between microbiota and IECs, enhancing defense mechanisms by fortifying IECs barrier function. In vitro it was shown that SCFAs stimulate transcription of genes for mucin in intestinal epithelial goblet cells (Loudon, Jones, and Sehmi 1992). These cells perform an important protective function as they produce mucins that lubricate and protect the epithelial intestinal surface and act as antigen-presenting cells (APCs) delivering luminal antigens to $CD103^+$ DC and promoting the development of regulatory T cells (McDole et al. 2012). This was also observed in vivo, in fact the colonization of GF mice with SCFA-producing Bacteroides Thetaiotaomicron or Faecalibacterium prausnitzii increased the production of mucus and goblet cell differentiation (Wrzosek et al. 2013). Among SCFAs, butyrate stimulates the IECs through the GPCR109A receptors to produce IL-18, a cytokine involved in the differentiation of $CD4^+$ T lymphocytes into Th 1, while *Bifidobacterium*-derived acetate would appear to have an anti-apoptotic effect on IECs (Fukuda et al. 2011; Kalina et al. 2002; Singh et al. 2014). The level of circulating innate cells, such as basophil, is also influenced by the microbiota, whose metabolites can influence basophil hematopoiesis (Hill et al. 2012).

Some lymphocytes belonging to innate immunity including innate lymphoid cells (ILCs) and gamma delta T cells ($\gamma\delta$T cells) are found in particular in barrier sites and peripheral tissues coordinating specific functions between host and microbiota. In particular, some commensal-induced cytokines as IL-1β and IL-23 promote the expansion of $\gamma\delta$T cells at barrier sites and the secretion of IL-17A involved in inducing and mediating pro-inflammatory responses and chemotaxis (Duan et al. 2010). The $\gamma\delta$T cells are particularly present in sites highly exposed to microbial products or metabolites, such as the liver (Kabelitz and Dechanet-Merville 2015). It was shown that microbiota promotes hepatic $\gamma\delta$T-17 cell homeostasis, including activation, survival, and proliferation and that in particular, Escherichia coli alone can generate $\gamma\delta$T-17 cells in a dose-dependent manner (Li et al. 2017). Among ILCs, particular attention has been given to ILC3 and its interaction with the microbiota. These cells often reside in proximity to exposed mucosal surfaces and produce IL-22, a master regulator of the intestinal barrier and intestinal stem-cell mediated regeneration of central importance in the maintenance of tissue immunity and physiology producing antimicrobial peptide, increasing mucus production and regulating wound repair (Eyerich, Dimartino, and Cavani 2017). Although further studies are needed on the connection between microbiota composition and ILC3 activation some evidence shows that segmented filamentous bacteria (SFB) colonization can promote IL-22 production by ILC3 (Sano et al. 2015).

Commensal bacteria play also a key role in regulating adaptive immunity and tolerance mechanisms (Belkaid and Harrison 2017). In fact, after interacting with the antigens expressed by pathogenic or resident bacteria, DC located under the IECs present them to the T lymphocytes, stimulating the T cell response and directing it toward an activation such as Th 1, Th 2, Th 17 or regulatory T cells (Tregs), or stimulate B lymphocytes to secrete Igs, especially IgA specific for commensal-derived antigens (Belkaid and Harrison 2017).

The induction of a mucous compartmented IgA response is ensured thanks to the interaction between DC and lymphocytes in the Peyer's patches, where the IgA-secreting B lymphocytes influenced by a microenvironment rich in cytokines and chemokines are selected and reached the lamina propria secrete IgA soluble that prevent the adhesion of commensal bacteria to the intestinal epithelium and modulate the bacterial gene expression (Boullier et al. 2009; Macpherson and Uhr 2004; Sutherland, Suzuki, and Fagarasan 2016). There is, therefore, a dialogue between intestinal microorganisms and secreting IgA B lymphocytes intestinal colonization promotes early B-cell development through the editing of B cell receptors within the lamina propria while IgA help to select and maintain a balanced microbiota (Wesemann et al. 2013). As mentioned, the commensal bacteria play a fundamental role in the differentiation of some lymphocyte classes: in fact, it was observed that GF mice, or treated with specific antibiotics, Th17 cells are severely reduced in the mucosa of the small intestine (Leigh et al. 1991) and that intestinal colonization by SFB or *Bifidobacterium adolescentis* promotes local Th17 cell differentiation (Tan et al. 2016). Th17 cells contribute by regulating intestinal physiology through the secretion of some cytokines as IL-17A, IL-17F, and IL-22 that can stimulate the production of antimicrobial peptides by IECs and reinforce epithelial cell tight junction (Weaver et al. 2013). Furthermore, as suggested by some evidences, the microbiota's ability to influence the immune system could have interesting oncological implications. Especially in hematological malignancies, total body irradiation is frequently used and involves gut damage and microbial translocation, which has been proven to provide an adjuvant effect to the antitumoral $CD8^+$ T cells (Paulos et al. 2007). Similarly, intestinal damage and microbial translocation caused by treatment with the alkylating agent cyclophosphamide also seem to contribute to the anticancer response by inducing some subtypes of lymphocytes such as Th17, Th1 and $\gamma\delta$T (Viaud et al., 2013). Therefore, given the fundamental role played by the intestinal microbiota in the modulation of the immune response and the onset and progression of pathologies on an autoimmune basis or not and considering that

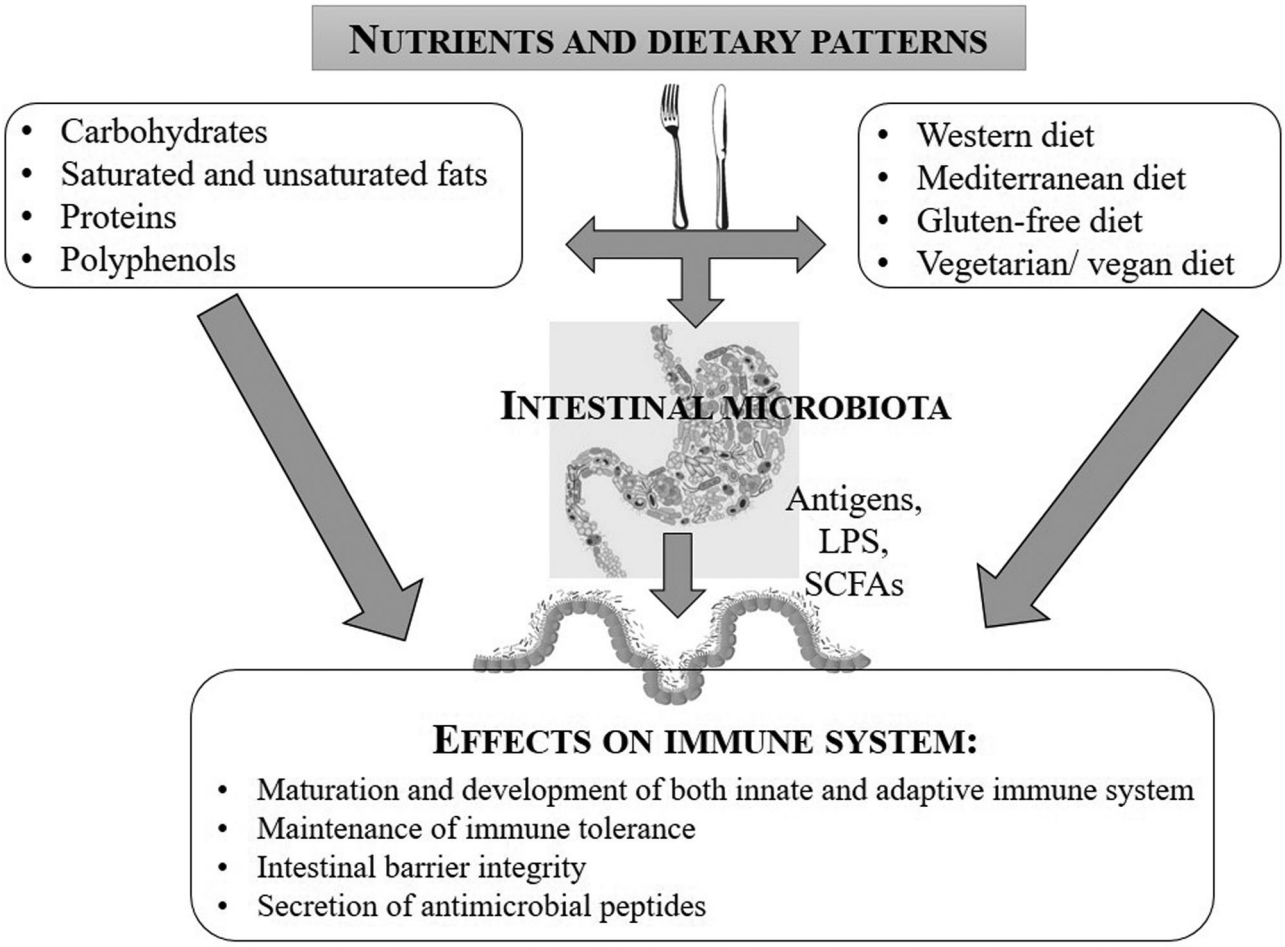

Figure 3. Interaction between diet, intestinal microbiota and immune system. The different macro and micronutrients as well as the food patterns influence the composition of the intestinal microbiota, which in turn through the release of antigens, LPS and SCFAs influences the immune system. Therefore intestinal microorganisms play a crucial role in the maturation and development of both innate and adaptive immune system, maintenance of immune tolerance, intestinal barrier integrity and secretion of antimicrobial peptides. LPS, lipopolysaccharide; SCFAs, short chain fatty acids.

diet represents one of the modifiable factors with the greatest impact on the composition of the microbiota, different nutritional patterns could represent useful therapeutic tools to be associated with standard immunomodulatory therapy in the treatment of specific pathologies.

The interaction among diet, intestinal microbiota and immune system is shown in Figure 3.

Mediterranean diet and immune function

A healthy and balanced diet is essential for the well-being and health of the organism and therefore also for the proper functioning of the immune system (Childs, Calder, and Miles 2019). A diet rich in high-quality foods such as those rich in whole grains, healthy lipids, natural antioxidants, and fiber can influence the activity of the innate immune system by reducing the production of pro-inflammatory cytokines and increasing that of anti-inflammatory cytokines (Esposito and Giugliano 2006). A dietary pattern that reflects these characteristics and that guarantees an adequate intake of high-quality food is represented by the MD.

The MD is a nutritional model that is based on the eating habits and traditional lifestyle typical of the Mediterranean country in the 1960s (Salas-Salvado, Becerra-Tomas, et al. 2018). The term was coined in the middle of the last century by Ancel Keys, an American biologist, and physiologist, promoter of the pioneering study "Seven Country Study," from which emerged a lower mortality rate from coronary heart disease in Mediterranean countries. These results were attributed to the typical diet of these populations rich in monounsaturated fats, PUFA and fibers, and poor in SFA, which represent the main dietary factor responsible for the increase in the levels of total cholesterol and LDL-cholesterol, both important cardiovascular disease (CVD) risk factors (Blackburn 2017; Estruch and Camafort 2015; Sandker et al. 1993).

The MD pattern is characterized by the high consumption of plant foods (cereals, fruits, vegetables, legumes, nuts, seeds, and olives), the moderate consumption of dairy products (mainly cheeses and low-fat yogurt), eggs (no more than four per week) and fish, the low intake of sweets and red meat, the moderate intake of alcohol (mostly red wine) with meals. Also, the main source of fat is represented by extra virgin olive oil, which is rich in bioactive compounds responsible for the high nutritional quality of this food (Mazzocchi et al. 2019). After the Seven Country Study, numerous other studies were carried out to investigate the beneficial effects of the MD on health, which confirmed the

cardiovascular benefits of this dietary pattern (Buckland et al., 2009; Martinez-Gonzalez et al. 2011; Vargas, Azarbal, and Tota-Maharaj 2020) and also showed that it is able to reduce the risk of developing other pathologies such as metabolic syndrome (Babio et al. 2009; Kesse-Guyot et al. 2013; Salas-Salvado et al., 2008), type 2 diabetes mellitus (InterAct et al., 20112013; Martinez-Gonzalez et al. 2008; Salas-Salvado, Bullo, et al. 2018), neurodegenerative diseases (de la Rubia Orti et al. 2018; Gardener and Caunca 2018), forms of cancer (Altieri et al. 2018; Barrea, Altieri, et al. 2018; Laudisio et al. 2020; Maruca et al. 2019; Milajerdi et al. 2018), chronic inflammatory skin diseases (Barrea et al. 2015; Barrea, Fabbrocini, et al. 2018), and endocrine diseases (Barrea, Arnone, et al. 2019; Muscogiuri, Barrea, Di Somma, et al. 2019; Muscogiuri, Barrea, Laudisio, et al. 2019).

The possible mechanisms underlying the pro-health and pro-longevity effects of the MD may be due to its anti-inflammatory and immune-modulating properties (Soldati et al. 2018; Tosti, Bertozzi, and Fontana 2018) that derive from the synergy between the various nutrients and foods that interact with each other potentiating their beneficial effects (Lacatusu et al. 2019). The MD is rich in substances with antioxidant and anti-inflammatory activity, such as monounsaturated fatty acids, omega-3 fatty acids, polyphenols, flavonoids, phytosterols, vitamins (β-carotene, vitamin C, vitamin E), minerals (such as selenium) and micronutrients (Di Daniele et al. 2017).

The evidence that the MD can positively influence the state of health through an anti-inflammatory action comes from various studies including a sub study of the *Prevención con Dieta Mediterránea* (PREDIMED) trial, in which the efficacy of the MD in the primary prevention of CVD was assessed comparing the effect of 3 dietary interventions (the MD integrated with extra virgin olive oil, the MD integrated with mixed nuts and low-fat diet) on inflammatory cellular and serum biomarkers related to atherogenesis in subjects with a high risk of CVD (Mena et al. 2009). After 3 months, subjects who followed both diet treatments consisting of a supplemented MD, unlike those who followed the low-fat control diet, showed a reduction in cellular and circulating inflammatory biomarkers, such as serum IL-6 and soluble intercellular adhesion molecule-1 (sICAM-1) (Mena et al. 2009). These results confirm those reported by another study in which it was shown that subjects with greater adherence to the MD showed lower concentrations of biomarkers of inflammation and endothelial dysfunction, like CRP-levels, IL-6, and e-selectin (Fung et al. 2005). Its anti-inflammatory effect has also been shown against other pathologies associated with a condition of chronic inflammation such as type 2 diabetes mellitus. A dietary trial conducted on patients with newly diagnosed type 2 diabetes mellitus followed for 8.1 years, showed that subjects randomized to follow the MD showed an improvement in inflammatory markers with a decrease in CRP levels and an increase in adiponectin levels, in association with an improvement in insulin resistance and glucose metabolism compared to those randomized to follow a low-fat diet (Maiorino et al. 2016).

One of the protagonists of this dietary model is represented by extra virgin olive oil, rich in antioxidant, anti-inflammatory and immune-modulating substances represented by monounsaturated fatty acids (especially oleic acid) and components of the unsaponifiable fraction (about 2% of the weight of the oil) such as polyphenols, phytosterols, tocopherols, and pigments (Aparicio-Soto et al. 2016). Polyphenols are secondary metabolites structurally characterized by multiple phenolic structures, known for their positive effect on health (Cicerale et al. 2009). They can reduce inflammation through various mechanisms, for example by acting as antioxidants, inhibiting the production of pro-inflammatory cytokines, suppressing inflammatory or inducing metabolic gene expression, or activating transcription factors that antagonize chronic inflammation (Bonaccio et al. 2017).

The main polyphenols olives are represented by tyrosol, hydroxytyrosol, oleocanthal, oleoresin, olives ligstroside, and oleuropein and among these, is the most studied for its anti-inflammatory properties. This latter represents only 10% of the olive's polyphenols (100–300 mg/kg olive oil) and is primarily responsible for the pungency and irritative sensation in the throat and oropharyngeal area typical of extra virgin olive oils (Gonzales et al. 1998; Smith et al. 2005). The oleocanthal inhibits the activity of enzymes involved in the inflammatory process such as cyclooxygenase (COX) 1 and 2, which catalyze the synthesis of prostaglandins, and also inhibits lipopolysaccharides-mediated up-regulation of pro-inflammatory signaling molecules, including IL-1β, IL-6, macrophage inflammatory protein-1α (MIP-1α), TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Parkinson and Keast 2014; Scotece et al. 2012).

The protective role of olive oil on the inflammatory status was, for example, highlighted in a study carried out by Fitò et al. in an adults population with stable coronary heart disease, which showed that the consumption of 50 ml of for 3 weeks leads to a reduction in IL-6 and CRP levels, also higher than those caused by the same dose of refined olive oil (Fito et al. 2008). Another study has shown that the intake of virgin olive oil based breakfast, rich in phenol compounds, an suppress the expression of various genes related to the inflammatory pathways in patients with metabolic syndrome, thereby switching activity of peripheral blood mononuclear cells to a less deleterious inflammatory profile and highlighting the importance of the phenolic fraction of this food (Camargo et al. 2010). Also oleic acid, a monounsaturated fatty acids present in high concentrations in extra virgin olive oil, seems to have anti-inflammatory properties that it exerts through the regulation of the expression of the pleiotropic genes involved in the signal transduction pathways and the production of cytokines (Oliviero et al. 2015). Furthermore, although a study has shown that the treatment with olive oil-based emulsion, rich in MUFA, leads to a reduction in lymphocyte proliferation and induces low toxicity to lymphocytes probably from necrosis (Cury-Boaventura et al. 2008), oleic acid seems to be able to

influence the activity of some leukocytes that contribute to the destruction of microorganisms. In fact, in vitro studies have shown that oleic acid is able to enhance neutrophil phagocytic capacity, to stimulate ROS production by neutrophils and macrophages and to increase fungicidal activity of these cells (Martins de Lima-Salgado et al. 2011; Padovese and Curi 2009).

The MD is also characterized by a high intake of fibers (2 times higher than that of a typical Western pattern diet which can act on the intestinal microbiota by modulating its composition, activity and consequently the production of metabolites that regulate the immune function and inflammatory pathways (Anderson et al. 2009; Cardoso Dal Pont et al. 2020; Venter et al. 2020). In particular, a high dietary fiber intake leads to an increase in the number of intestinal bacterial species responsible for the production of SCFAs such as acetate, propionate, and butyrate (Barrea, Muscogiuri, Annunziata, Laudisio, Pugliese, et al. 2019; Tan et al. 2014; Thorburn, Macia, and Mackay 2014), important for the proper functioning of the immune system and in the prevention of inflammatory diseases (Thorburn, Macia, and Mackay 2014). The SCFAs are, in fact, able to modulate the immune cell chemotaxis and activity, and the release of ROS and cytokine (Tan et al. 2014). For example, butyrate can reduce the production of pro-inflammatory molecules such as TNF-α, IL-1β, and nitric oxide, reduce the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), inhibit the production of IL-12 and increase the production of IL-10 by monocytes (Ni et al. 2010; Saemann et al. 2000).

The MD also ensures a high intake of omega-3 PUFA from fish (such as mackerel, herring, and sardines), and vegetable (such as green plant tissues, vegetable oils like soybean and canola oils, nuts and seeds like flaxseeds) sources and an adequate omega-6/omega-3 ratio (Casas, Sacanella, and Estruch 2014) by promoting a better inflammatory profile compared to other Western pattern diet in which the intake of omega-6 fatty acids is greater and favors a higher production of pro-inflammatory cytokines and procoagulant factors that increase the risk of chronic diseases such as diabetes mellitus and atherosclerosis (Marklund et al. 2019; O'Mahoney et al. 2018; Schwingshackl, Morze, and Hoffmann 2020). Dietary omega-3 fatty acids have, in fact, a variety of anti-inflammatory and immune-modulating effect and seem to be able to reduce the inflammatory process in different ways, for example by acting on the leucocyte chemotaxis, adhesion molecule expression and leucocyte–endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the acid arachidonic, and production of inflammatory cytokines like TNF-α and IL-1β (Calder 2017). From omega-3 PUFAs are also produced anti-inflammatory molecules known as specialized pro-resolution mediators (SPM), which includes resolvins, produced from EPA and DHA, proteins and maresins that are produced by DHA. SPMs bind to specific receptors and contribute to the resolution of the inflammatory process by increasing the efferocytosis, phagocytosis, and leukocytes egress (Back and Hansson 2019; Parolini 2019).

In addition to the aforementioned anti-inflammatory effects, the beneficial impact on health of the MD could also be due to its ability to modulate the immune system. In the study previously seen conducted by Mena et al. on a population of subjects at high risk of CVD, it was found that after three months from the beginning of the dietary intervention, the subjects who followed a MD integrated with virgin olive oil or nuts showed not only a reduction in IL-6 and sICAM-1, inflammation mediators important in the adhesion of leukocytes to the endothelial surface, but also a reduction in the immune cells activation biomarkers related to the atherosclerotic process. In particular, there was a reduction in the expression of the pro-inflammatory ligand CD40 and the adhesion molecule CD49d on T lymphocytes and monocytes, after both MD but not after the low-fat diet (Mena et al. 2009).

Several components of the MD are, in fact, capable of regulating the function the immune system cells, such as omega-3 PUFAs (Galli and Calder 2009; Kim et al. 2010; Wu et al. 2018).

Omega-3 PUFAs could in fact modulate the function of T cells either directly, for example by inhibiting the differentiation of Th1 and Th17, or indirectly by inhibiting the function of antigen-presenting cells like monocytes/macrophages and DC (Wu et al. 2018). It seems that they are also able to modulate the functions of B cells by promoting their activation and production of cytokines and antibodies, and for this reason integration with omega-3 PUFAs could be useful in more patients with an altered humoral immune response, such as aging population (Gurzell et al. 2013; Teague et al. 2014; Whelan, Gowdy, and Shaikh 2016; Wu et al. 2018).

In addition, the intake of polyphenols appears to be associated with a change in the count and differentiation of immune cells (Yahfoufi et al. 2018). They, for example, downregulate macrophage activity thereby reducing the production of TNFα, IL-1-β and IL-6 expression (Gonzalez et al. 2011) and affect Th cell populations. Wang et al. in fact, highlighted that the epigallocatechin gallate inhibited differentiation of naïve $CD4^+$ T cells into pro-autoimmunity subsets Th1, Th17, and Th9, that are involved in development of some autoimmune disease, and prevented IL-6-induced suppression of Treg development in mice (Wang et al. 2013). Resveratrol, another polyphenol found in red grapes, also appears to be capable of regular innate and adaptive immunity in a dependent dose, stimulating the low-dose immune response and inducing high-dose immunosuppression (Malaguarnera 2019).

The interaction among some single foods of the MD with immune system is illustrated in Figure 4.

Functional supplements and immune function

The MD is characterized by nutrient-rich foods (such as vitamins and minerals) with antioxidant and anti-inflammatory properties and low in refined starches, saturated and trans-fatty acids; this dietary pattern may cause an up-regulation of the innate immune system, most likely by the

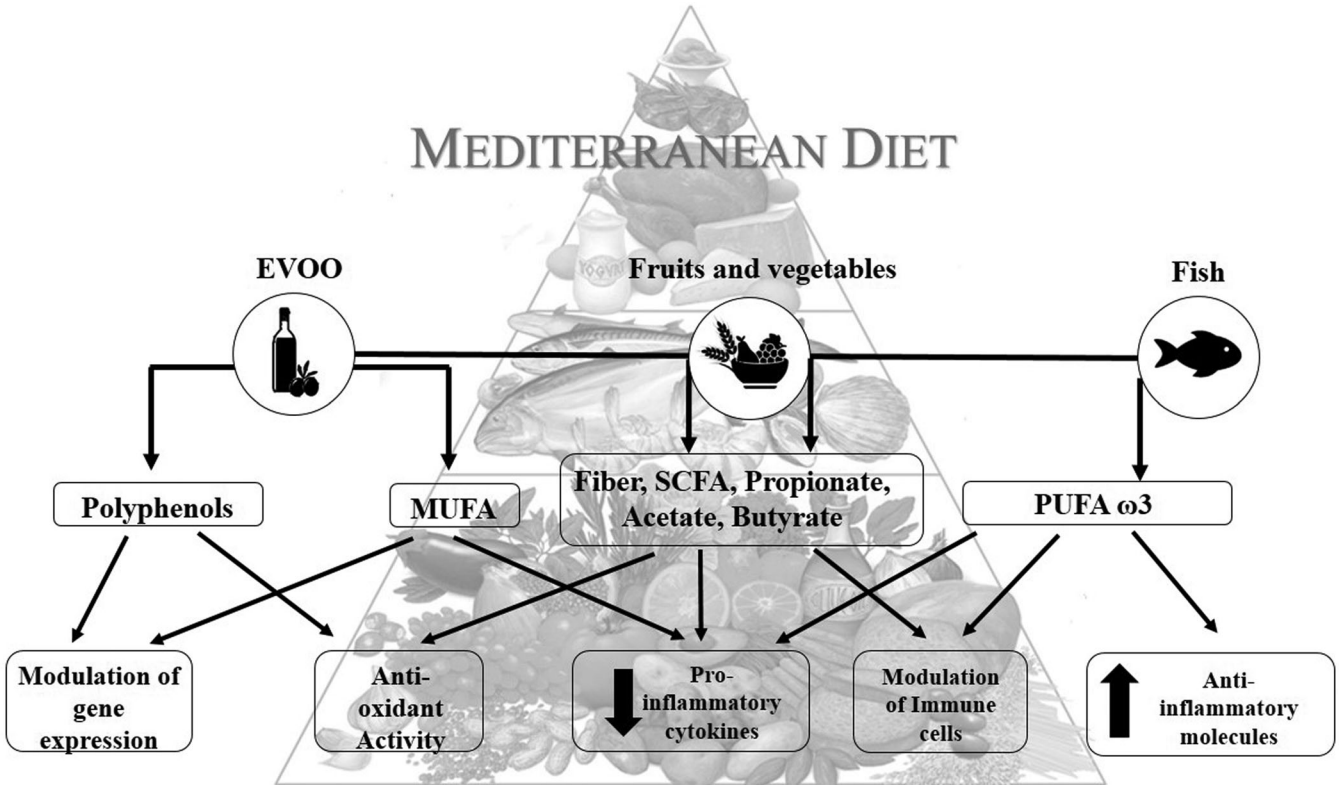

Figure 4. The interaction among some single foods of MD with immune system. MD, Mediterranean diet; EVOO, extra virgin olive oil; MUFA, monounsaturated fatty acids; SCFA, short chain fatty acids; PUFA, polyunsaturated fatty acids.

production of anti-inflammatory cytokines (Casas, Sacanella, and Estruch 2014; Castiglione et al. 2018). Although the MD could be considered an ideal nutritional approach to boost immune function, it is often difficult to be followed, mostly in subjects with obesity (Pittler and Ernst 2004). In this context, dietary supplements may be perceived as an "easy solution," that is less demanding than lifestyle changes (Barrea, Altieri, et al. 2019). Despite some dietary supplements are costly, their use has increased greatly, thereby becoming of considerable interest for nutritionists (Marik and Flemmer 2012). The effectiveness and safety of the use of dietary supplements is still a highly debated issue (Dwyer, Coates, and Smith 2018).

With the term dietary supplement means "a product (other than tobacco) intended to supplement the diet that bears or contains 1 or more of the following dietary ingredients: (a) a vitamin, (b) a mineral, (c) an herb or other botanical, (d) an amino acid, (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or (f) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)," according to Dietary Supplement Health and Education Act (Wong et al. 2016). Dietary supplements, generally taken orally and found as capsules, tablets, liquids, or powders, are therefore, products intended to supplement the diet and not substitute it (Barrea, Altieri, et al. 2019).

Some dietary components also known as phytochemicals have very important roles in the development and maintenance of an effective immune system or in the decrease of chronic inflammation (Calder 2015; Dankers et al. 2016; Meydani et al. 2004; Turchet et al. 2003).

Nutrients that can be considered functional foods, that exert physiological benefits on immune function are: dietary lipids such as PUFA, micronutrients (vitamins D and E, zinc, selenium), and probiotics, for their immunological effect, working mechanisms and clinical relevance. Several micronutrients acting also synergistically each other, are essential to the immune system (Gombart, Pierre, and Maggini 2020).

Omega-3 PUFAs

Many dietary lipids are energy-providing macronutrients that are able of regulating several cell functions. The impact of PUFAs dietary intake with special focus on the omega-3 PUFAs ALA, EPA, and DHA on the immune system has been recently detailed by Gutiérrez S. et al. (Gutierrez, Svahn, and Johansson 2019). Nuts and seeds are particularly rich in ALA, whereas the fish oil contains EPA and DHA (Gutierrez, Svahn, and Johansson 2019). From ALA through a process with different steps orchestrated by multiple elongases, desaturases, and β-oxidases (Wiktorowska-Owczarek, Berezińska, and Nowak 2015), both DHA and EPA can be synthesized (Calder 2016); nevertheless, the synthesis of this latter from ALA is at a low rate in mammals (Metherel et al. 2018). In particular, omega-3 PUFAs derived by a marine animal, such as EPA and DHA have shown to modulate both innate and adaptive immunity (Calder 2017; Kim et al. 2010; Whelan, Gowdy, and Shaikh 2016). The

Table 1. Role in immune function and recommended intakes of main nutrients, according to SINU and EFSA.

Functional supplements	Role in immune function	Recommendations	References
Omega-3 PUFA (EPA-DHA)	Inhibits pro-inflammatory mediators as pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), eicosanoids (PGE2, 4-series leukotrienes), adhesion molecules (ICAM-1, VCAM-1, selectins), chemokines (IL-8, MCP-1), platelet-activating factor (PAF), and ROS and nitrogen species Increase the production of an anti-inflammatory cytokine such as IL-10 Inhibits NF-κB.	SINU 250 mg/day In both males and females, children and adults EFSA 250 mg/day In both males and females, children and adults	(SINU 2014d) (EFSA 2002b
Vitamin D Ergocalciferol (vitamin D_2) and Cholecalciferol (vitamin D_3)	Maintains of structural and functional integrity of mucosal cells in innate barriers; Regulates antimicrobial proteins (cathelicidin and β-defensin), responsible for modifying intestinal microbiota to a healthier composition; Inhibits IFNγ and IL2 production; Inhibits T-cell proliferation; Suppresses antibody production by B cells; Increases differentiation of monocytes to macrophages; Promotes movement and phagocytic ability of macrophages.	SINU 10 μg/day infants (6–12 months) 15 μg/day in children (male and female) 15–20 μg/day in adult (males and females) 20 μg/day in elderly $\geq$75 years 15 μg/day in pregnancy EFSA 10 μg/day infants (7–11 months) 15 μg/day in both males and females, children and adults	(SINU 2014c) (EFSA 2002b)
Vitamin E (α-tocopherol)	Protects cell membranes from damage caused by free radicals and support the integrity of epithelial barriers; Inhibits PGE2 production by macrophages, with indirectly protecting T-cell function, enhances IL-2 production and maintains or enhances NK cell cytotoxic activity; Important fat-soluble antioxidant that hinders the chain reaction induced by free radicals (chain-breaking effect) and protects cells against them	SINU 4 mg/day infants (6–12 months) 5–13 mg/day in children (male and female) 13 mg/day in adult males 12 mg/day in adult females 15 mg/day in pregnancy EFSA 5 mg/day infants (7–11 months) 6–13 mg/day in children male 5–11 mg/day in children female 13 mg/day in adult males 11 mg/day in adult females	(SINU 2014c) (EFSA 2002b)
Vitamin B6 (Niacin)	Maintains or enhances NK cell cytotoxic activity; Involved in lymphocyte proliferation, differentiation, maturation, and activity.	SINU 0.4 mg/day infants (6–12 months) 0.5–1.3 mg/day in children (male and female) 1.3–1.7 mg/day in adult males 1.3–1.5 mg/day in adult females 1.9 mg/day in pregnancy EFSA 0.3 mg/day infants (7–11 months) 0.6–1.7 mg/day in children male 0.6–1.6 mg/day in children female 1.7 mg/day in adult male 1.6 mg/day in adult female 1.5 mg/day in pregnancy	(SINU 2014c) (EFSA 2002b)
Vitamin B12 (Cobalamin)	Immunomodulator for cellular immunity, effects on cytotoxic cells (e.g., NK cells, cytotoxic T cells); Facilitates production of T cells such as cytotoxic T cells.	SINU 0.7 μg/day infants (6–12 months) 2.2–2.4 μg/day in children (males and females) 2.4 μg/day in adult (males and females) 2.6 μg/day in pregnancy EFSA 1.5 μg/day infants (7–11 months) 1.5–4 μg/day in children (male and female) 4 μg/day in adult (males and females) 4.5 μg/day in pregnancy	(SINU 2014c) (EFSA 2002b)
Vitamin B9 (Folate)	Maintains or enhances NK cell cytotoxic activity	SINU 110 μg/day in infants (6–12 months) 350–400 μg/day in children (male and female) 400 μg/day in adult (males and females) 400 μg/day in pregnancy EFSA 80 μg/day in infants (7–11 months) 120–330 μg/day in children (male and female) 330 μg/day in adult (males and females) 600 μg/day in pregnancy	(SINU 2014c) (EFSA 2002b)
Zinc	Maintains or enhances NK cell cytotoxic activity;	SINU 3 mg/day in infants (6–12 months)	(SINU 2014d)

(*continued*)

Table 1. Continued.

Functional supplements	Role in immune function	Recommendations	References
	Anti-inflammatory action; Helps to modulate cytokine release by dampening the development pro-inflammatory Th1 cells and influencing the generation of NK cell and cytokines such as IL-2, IL-6, and TNF-α.	12 mg/day in children male 9 mg/day in children female 12 mg/day in adult males 9 mg/day in adult females 11 mg/day in pregnancy	
		EFSA 2.9 mg/day in infants (7–11 months) 4.3–14.2 mg/day in male children 4.3–11.9 mg/day in female children 9.4–16.3 mg/day in male adults 7.5–12.7 mg/day in female adults 14.3 mg/day in pregnancy	(EFSA 2002b)
Selenium	Essential for function of selenoproteins that act as redox regulators and cellular antioxidants, potentially counteracting ROS produced during oxidative stress	SINU 20 μg/day in infants (6–12 months) 55 μg/day in children and adults (male and female) 60 μg/day in pregnancy	(SINU 2014d)
		EFSA 15 μg/day in infants (7–11 months) 15–70 μg/day in children (male and female) 70 μg/day in adult (males and females) 70 μg/day in pregnancy	(EFSA 2002b)

IL, Interleukin; TNF, tumor necrosis factor; PGE2, prostaglandin E2; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; MCP-1, monocyte chemoattractant protein-1; PAF, platelet-activating factor; ROS, reactive oxygen species; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IFNγ, interferon γ; NK, natural killer; Th; T helper cells.

omega-3 PUFAs inhibit pro-inflammatory mediators as pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), eicosanoids (Prostaglandin E2, 4-series leukotrienes), adhesion molecules (sICAM-1, vascular cell adhesion molecule 1 (VCAM-1), selectins), chemokines (IL-8, monocyte chemoattractant protein-1 (MCP-1), platelet-activating factor (PAF), and ROS and nitrogen species (Lordan, Tsoupras, and Zabetakis 2017; Parikh et al. 2019; Pauls et al. 2018); moreover, they increase the production of an anti-inflammatory cytokine such as IL-10 (Sierra et al. 2006). It has been demonstrated that omega-3 PUFAs has a role in the modulation of gene activation omega-3 PUFAs inhibits NF-Kb signaling and so it interferes with the TLR4 pathway and its receptor protein MyD88, activating omega-3 PUFAs membrane receptor GPR120, and act as ligands to bind to and activate the peroxisome proliferator-activated receptor gamma (PPAR-γ), an anti-inflammatory transcription factor that can trans-repress NF-κB activation (Mullen, Loscher, and Roche 2010; Zhao et al. 2004). Furthermore, omega-3 PUFAs intake inhibits mitogen or T cell antigen receptor activation-induced l lymphocyte and CD4 T cell proliferation, IL-2 production, and IL-2 receptor expression, and the antigen-driven CD4 T cell expansion in animal studies (Fan et al. 2004; Switzer et al. 2004). The inhibiting property of the T cells is attributed to increase lipid peroxidation, modulation of membrane phospholipid composition, cytoskeletal structure, and disruption of lipid rafts (Fan et al. 2018). Animal models and human studies reported a beneficial role of omega-3 PUFAs in the modulation of chronic inflammation. The protective action of omega-3 PUFAs has been reported in conditions of chronic inflammation such as asthma, inflammatory bowel disease, Crohn's disease, and ulcerative colitis, and also in autoimmune disorders (Calder 2015, 2017; Galli and Calder 2009).

Although the mechanisms of action of omega-3 fatty acid on immune cells function have several cell type-specific features, omega-3 fatty acids *via* dietary supplementation, incorporate effectively, into the cellular membrane of all the immune cells, regulate immune processes (Gutierrez, Svahn, and Johansson 2019).

The RDA according to The Italian Society of Human Nutrition, SINU- *Società Italiana di Nutrizione Umana* (SINU 2014a) is 250 mg/day for omega-3 EPA-DHA in all children, adults and older age, males and females respectively (SINU 2014b).

Otherwise, the European Food Safety Authority (EFSA) considers The Population Reference Intake (PRI) "*which is the level of (nutrient) intake that is adequate for virtually all people in a population group*" (EFSA 2002a).

According to EFSA, the PRI for omega-3 fatty acids EPA-DHA is 250 mg/day in all children and adults, males and females, respectively (EFSA 2002b); Table 1.

Vitamin D

The vitamin D has long been recognized as the vitamin involved in bone homeostasis, but, currently, there are growing evidence that point out its extra-skeletal effects (Barrea, Muscogiuri, Annunziata, Laudisio, de Alteriis, et al. 2019; Barrea, Muscogiuri, Laudisio, et al. 2019; Grubler et al. 2017; Marino and Misra 2019; Martens et al. 2020; Muscogiuri, Barrea, Altieri, et al. 2019; Savanelli et al. 2016). Indeed, vitamin D can also significantly influence the adaptive immune function (Bobeck 2020; Provvedini et al. 1983; Wessels and Rink 2020). Vitamin D performs several functions in immune regulation, in particular, it plays a role in maintaining structural and functional integrity of mucosal

cells in innate barriers, it takes part in the differentiation, proliferation and function of innate immune cells and of T cells, antibody production and development, and responses to an antigen (Gombart, Pierre, and Maggini 2020). Further, vitamin D has several other roles in the immune system as antimicrobial, anti-inflammatory, and antioxidant effects. Finally, vitamin D takes part in differentiation of the cells of the immune system (Gombart, Pierre, and Maggini 2020). Vitamin D receptor (VDR) has been detected in both T and B cells and vitamin D-activating enzymes, and vitamin D itself are commonly inhibitory on both T and B cells (Lemire et al. 1984). In particular, vitamin D inhibits T cell proliferation and effector functions of $CD4^+$ and $CD8^+$ T cells (Rigby, Stacy, and Fanger 1984) and inhibits the production of IL-2 and IFN-γ, both two important T cell cytokines. Moreover, vitamin D suppresses antibody production by B cells (Gombart, Pierre, and Maggini 2020). It has been shown that vitamin D has an effect on APC function, especially through DC (Bscheider and Butcher 2016). In fact, VDR was found in monocytes, macrophages, and DC and it increases differentiation of monocytes to macrophages (Gombart, Pierre, and Maggini 2020). Vitamin D can inhibit DC differentiation from their bone marrow and monocytes precursor cells, and also their maturation (Penna and Adorini 2000) and promotes phagocytic ability of macrophages (Gombart, Pierre, and Maggini 2020). Vitamin D also regulates cathelicidin and β-defensin (antimicrobial proteins) leading to support the gut barrier increasing the E-cadherin (tight junction protein expression), and modify of the gut microbiota to a healthier composition (Clark and Mach 2016). Again, vitamin D increases the expression of anti-inflammatory cytokines by macrophages and reduces the expression of pro-inflammatory cytokines (Gombart, Pierre, and Maggini 2020). Therefore, vitamin D could be considered a therapeutic potential application in the clinic to alleviate autoimmune and inflammatory diseases. In animals studies vitamin D supplementation prevent or relieve inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis rheumatoid arthritis, and type 1 diabetes (Colotta, Jansson, and Bonelli 2017; Dankers et al. 2016). Although these encouraging findings, there are still trials that report inconsistent results on the effect of vitamin D supplementation on incidence and severity of autoimmune diseases (Agmon-Levin et al. 2013; Antico et al. 2012).

In some meta-analyses, the supplementation of vitamin D (300–3653 IU/day) in adults and children has been shown to reduce the risk of respiratory tract infections (Autier et al. 2017; Rejnmark et al. 2017). Evidence suggest that the supplementation of vitamin D could have potential benefits in adults and children with respiratory tract infections (Yamshchikov et al. 2009).

The RDA for vitamin D for SINU and EFSA is 15 µg/day in children and adults (EFSA 2002b; SINU 2014c), and 15–20 µg/day in both males and females older age (SINU 2014c); Table 1.

Vitamin E

Vitamin E is a fat-soluble physiological antioxidant and includes all tocopherols and tocotrienols with the similar biological activity of α-tocopherol (de Mello et al. 2008). Vitamin E protect from oxidative damage related to high metabolic activity by lipoperoxyl radical scavenging activities, protect cell membranes from damage caused by free radicals and support the integrity of epithelial barriers (Lee and Han 2018).

Vitamin E preserve membrane integrity, modulate the signaling events in T cells, protecting T cell function indirectly by reducing the production of T cell-suppressing factors such as prostaglandin E2 from macrophages (Wu and Meydani 2008). Prostaglandin E2 has several effects in both the innate and adaptive immune system, in particular, inhibiting T cell proliferation, IL-2 production, and IL-2 receptor expression (Kalinski 2012). The suppressive effect of prostaglandin E2 on T cells involves inhibition of different early signaling events that occur after T cell activation and for some of them, vitamin E can prevent prostaglandin E2-induced inhibition (Kalinski 2012). Moreover, vitamin E has anti-inflammatory and antioxidant effects by inhibiting the enzymatic activity of COX, signal transducer and activator of transcription-3, NF-κB, TNF-α, cytokines as IL-1, IL-6, IL-8, and inducing nitric oxide synthase, superoxide dismutase, quinone oxidoreductase, glutathione peroxidase (Beharka et al. 2002; Lee and Han 2018). Studies in animal models have shown the protective effects of vitamin E on the infection (Bou Ghanem et al. 2015; Han et al. 2000; Hayek et al. 1997). In older people, vitamin E supplementation was associated with better T-cell function (Gombart, Pierre, and Maggini 2020) and a better vaccine efficacy (Meydani et al. 1997). However, few studies have directly examined the effect of vitamin E supplementation on infection in humans. In a randomized controlled trial, Meydan et al. showed a protective effect of vitamin E supplementation of 200 mg/day on upper respiratory tract infections, particularly the common cold, compared to those receiving the placebo (Meydani et al. 2004). Furthermore, studies show inconsistent and controversial results, in particular, the results from the Alpha-Tocopherol Beta Carotene Cancer Prevention studies showed positive, no effect, and even negative effect of vitamin E on pneumonia and the common cold depending on the age (1994; Hemila and Kaprio 2011; Hemila et al. 2006). However, the discrepant results can be attributed to the confounding factors such as the difference in health conditions of participants and the intervention protocols.

The RDA recommended by SINU for vitamin E is 7–15 mg/day in children and 15 mg/day in both adults and older age, males and females (SINU 2014c). The PRI recommended by EFSA for vitamin E in children is 6–13 mg/day for boys and 5–11 mg/day for girls, while in adults is 13 mg/day and 11 mg/day for males and females, respectively (EFSA 2002b); Table 1.

Vitamins of group B

The vitamins that belong the B group are 8 (B_1, B_2, B_3, B_5, B_6, B_8, B_9, B_{12}), and have several functions, but, they are mainly co-factors to enzymes involved in energy metabolism and in the synthesis of organic molecules. Moreover, acting

as one carbon donors in nucleotide synthesis and the methylation of proteins and the DNA, in particularly folic acid, B_6 and B_{12}, they play an important role for the immune system (Depeint et al. 2006). Up-regulating NK cells and $CD8^+$ T cells, vitamin B_{12} plays an important role for the cytotoxic immune response mediated by both cells (Tamura et al. 1999). Moreover, vitamin B_6 has immune-regulatory properties and studies on rats have showed that its deficiency results in thymic atrophy and lower activity of thymulin (Chandra, Heresi, and Au 1980; Doan 1977). In addition, vitamin B_6 deficiency inhibited the proliferation of lymphocytes and interfered with their differentiation (Qian et al. 2017). Finally, also folate deficiency showed negative effects on immune functions and its deficiency is associated with reduced maturation of DC, and a lower secretion of IL-12, IL-6, and IL-1β after DC stimulated with LPS and impaired differentiation of $CD4^+$ T lymphocytes (Wu, Huang, and Lin 2017). In the Framingham Offspring study, the subjects with the lowest levels of pyridoxal 5′-phosphate, the active form of vitamin B_6, had the highest levels of chronic inflammation, evaluated by an overall inflammation score (IS) as the sum of standardized values of 13 individual inflammatory markers, instead the subjects with highest levels of pyridoxal 5′-phosphate had the lowest inflammation scores (Sakakeeny et al. 2012). In the elderly vitamin B_6 deficiency is associated with impaired Th cell functions and IL-2 production. Moreover, immune response in patients with critically ill (Cheng et al. 2006) and renal failure (Casciato et al. 1984) improved by supplementation with pyridoxine.

The RDA and PRI for vitamins of group B according to SINU and EFSA were reported in Table 1 (EFSA 2002a; SINU 2014c).

Zinc

Zinc is an important micronutrient for maintaining homeostasis of the immune system, in fact its deficiency has a negative impact on immune functions. Studies have shown that zinc deficiency, determines a thymus involution and reduced number of Th1 cells, as well as impaired immune functions including lymphocyte proliferation, antibody response, NK cell activity, IL-2 production, delayed-type hypersensitivity response, macrophage phagocytic activity, and impairing the chemotactic responses of neutrophils (Haase and Rink 2009; Mitchell et al. 2006; Mocchegiani and Malavolta 2004). Instead, supplementation of zinc can reverse impairment in the immune system and reduce mortality from infectious diseases (Fischer Walker and Black 2004; Haase and Rink 2009). Children and the elderly are populations at high risk for zinc deficiency, and this condition is associated with the compromised immune function and contributing to the increased morbidity and mortality from infections in these populations (Bideci et al. 2005). In a systemic review, Yakoob et al. reported that preventive zinc supplementation, in children (3 months to 5 years) of developing countries, was associated with a reduction in diarrhea and pneumonia morbidity and mortality in children (Yakoob et al. 2011). Indeed, in a systematic review, Hemila et al. showed that the duration of the common cold may be reduced in children and adults after supplementation of zinc >75 mg/day, but not at lower doses (Hemila 2011).

According to SINU, the RDA for zinc is of 11–9 mg/day in children, males and females respectively, and 11–8 mg/day in both adults and older age, males and females respectively (SINU 2014d). According to EFSA, PRI for zinc in children is 4.3–14.2 mg/day for boys and 4.3–11.9 mg/day for girls, in adults is 9.4–16.3 mg/day for males and 7.5–12.7 mg/day for females (EFSA 2002b); Table 1.

Selenium

Selenium deficiency can determine the reduction of immune-incompetence and consequently increased susceptibility to infections and possibly to cancers, infact, selenium reduce the frequency of DNA adducts and chromosome breaks, and reduce the detrimental mutations that contribute to carcinogenesis, and also, increase the activity of repair enzymes such as DNA glycosylases and DNA damage repair pathways that involve p53, BRCA1 and Gadd45 (Avery and Hoffmann 2018; Bera et al. 2013). Animal studies showed that selenium could modulate the pathology that accompanies chronic diseases in the gut and liver such as colitis and chronic liver injury, and cancer-related inflammation. Moreover, determines higher levels of inflammatory cytokines in several tissues as the uterus (Zhang et al. 2015), mammary gland tissues (Gao et al. 2016), and gastrointestinal tract (Barrett, Short, and Williams 2017; Nettleford and Prabhu 2018). In addition, selenium has an important role in thyroid autoimmunity, in fact, severe selenium deficiency, increased the risk of chronic autoimmune thyroiditis (Hu and Rayman 2017; Wu et al. 2015). Autoimmune thyroiditis is characterized by lymphocytic infiltration of the thyroid gland and the presence of circulating thyroid autoantibodies (Ajjan and Weetman 2015), and several evidence by epidemiological studies showed that selenium/selenoproteins can reduce thyroid peroxidase antibody titers, hypothyroidism, and reduce the incidence of postpartum thyroiditis (Ajjan and Weetman 2015; Combs et al. 2009); probably, by anti-inflammatory and immunomodulatory potential properties of selenium (Hu and Rayman 2017).

Considering that diet alone may be insufficient, a tailored micronutrient supplementation based on specific age-related needs necessary. Thus, although, existing data are still scarce, the overall available body of evidence suggests that supplementing the diet with immune-supportive micronutrients, such as selenium and zinc, may help to optimize immune function and reduce the risk of infection. Furthermore, also the selenium is an important component of several enzymes involved in redox reactions, thus, is an essential element for the immune system by protecting immune cells as phagocytes from oxidative stress, and at the same time, allowing for the physiological roles of ROS as signal transducers and microbicidal agents (Hoffmann 2007).

According to SINU, the RDA for selenium is of 55 µg/day in all children, adults and older age, males and females respectively (SINU 2014d). According to EFSA, PRI for selenium in children is 15–70 μg/day for both boys and girls, while in adults is 70 μg/day in males and females (EFSA 2002b).

Table 1 report the main roles of nutrients on immune function, and recommended intakes of nutrients to support optimal immune function, according to SINU and EFSA, divided by gender.

Probiotics

Probiotics have been defined by The World Health Organization as "*live microorganisms which when administered in adequate amounts confer a health benefit on the host*"(Mack 2005), and they can modulate immune and inflammatory response in the gut by the interaction with intestinal epithelial cells, M-cells in Peyer's patches and DC (Baba et al. 2009; Macpherson and Uhr 2004; Rescigno et al. 2001; Terpou et al. 2019). Probiotics induce pro-inflammatory cytokines to support immune response against infection and also induce anti-inflammatory cytokines to mitigate the excessive inflammatory response bringing to balanced homeostasis (La Fata, Weber, and Mohajeri 2018; Thomas and Versalovic 2010). Different evidence has shown that consuming probiotics induces IFN-α (Arunachalam, Gill, and Chandra 2000), reduces TNFα (Kekkonen et al. 2008) and IL-2 (Kekkonen et al. 2008), and does not affect IFN-γ, IL-1β, and IL-2 (Spanhaak, Havenaar, and Schaafsma 1998). Furthermore, probiotics has been also reported to have antiviral properties by increasing the cytotoxic potential of NK cells and the macrophage phagocytosis capacity. It has been shown that lipoteichoic acid, a cell wall component of Gram-positive bacteria (Bifidobacterium spp or Lactobacilli) by macrophages through the secretion of TNF-α that induces an increase in the configuration of important phagocytosis receptors such as FcγRIII and TLRs (Dongarra et al. 2013; Sommer and Backhed 2013). Besides, probiotics can interact with intestinal epithelial cells, by indirect effects on biofilms and direct impact by enhancing dam function by increasing tight junction and production of mucin, induction of antimicrobial peptides, and modulating the pro-inflammatory, immune-modulatory cytokines, and interfering with pathogenesis (Yousefi et al. 2019). Probiotics have been shown to enhance the host's resistance against infection. In a randomized controlled trial, Turchet et al. evaluated the effect of supplementation for 3 weeks with milk fermented with yogurt cultures and *L. casei DN-114001* on the incidence and severity of winter infections (gastrointestinal and respiratory) in elderly people (n = 360). They reported that the length of all viral infections was significantly lower in the treatment group (Turchet et al. 2003). Subsequently, this result was confirmed in a larger trial Multicentric, double-blind and controlled, in which healthy elderly (n = 1.072) received milk fermented with yogurt cultures (L. bulgaricus & S. thermophilus) and L. casei DN114001 (2×1010 CFU/d) for 3 months (Guillemard et al. 2010). The results showed that, when considering all common infectious diseases such as respiratory and gastrointestinal infections, community-acquired, the fermented product significantly reduced the average duration per episode of common infectious diseases and their cumulative duration. Indeed, the reduction in both episodes and cumulative durations was also significant for all upper respiratory tract infections and rhinopharyngitis (Guillemard et al. 2010). However, actually, for those positive effects observed, the exact working mechanisms have not been well elucidated. Moreover, these effects of probiotics are related to their property to compete with pathogenic microorganisms in the gut for nutrients and attachment to the gut epithelium, and regulating immune cell functions to remove infection and preventing excessive response and inflammation.

Conclusion

Nutritional interventions, especially the MD and its single beneficial components with specific antioxidant and anti-inflammatory actions, have the potential to improve and modulate the immune system. Although conflicting evidence exists, available results indicate that dietary supplementations with some nutrients including vitamin D and zinc may modulate immune function. Studies on the effectiveness of supplementation of single nutrients on improving the immune function are still limited and these have numerous methodological limitations, several are of low quality, and do not report efficacy and safety results. So, any supplementation should be decided by the nutritionist and used within recommended safety limits. Clinical studies of dietary patterns, single nutrients, and/or modifications of the microbiota on the immune system, have to be performed to fully understand the role of diet and nutrition on the regulation of the immune system.

Abbreviations

$\gamma\delta$T cells	gamma delta T cells
ALA	α-linolenic acid
APC	antigen-presenting cell
BF	Burkina Faso
BMI	body mass index
CD	cluster of differentiation
COX	cyclooxygenase
CRP	C-reactive protein
CVD	cardiovascular disease
DC	dendritic cell
DHA	docosahexaenoic acid
EAE	experimental autoimmune encephalomyelitis
EFSA	European Food Safety Authority
EPA	eicosapentaenoic acid
EU	European children
FOXP	forkhead transcription factor
GALT	gut-associated lymphoid tissue
GF	germ-free
GFD	gluten-free diet
GM-CSF	granulocyte-macrophage colony-stimulating factor
GPCR	G-protein-coupled receptor
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein

IEC	intestinal epithelial cell
IFN	interferon
Ig	immunoglobulin
IL	interleukins
ILC	innate lymphoid cell
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MCP	monocyte chemoattractant protein
MD	Mediterranean diet
MIP-1α	macrophage inflammatory protein-1α
NAFLD	nonalcoholic fatty liver disease
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	natural killer
PAF	platelet-activating factor
PAMP	pathogen associated molecular patterns
PPAR-γ	peroxisome proliferator-activated receptor gamma
PRI	Population Reference Intake
PUFA	polyunsaturated fatty acid
RDA	recommended daily allowance
ROS	reactive oxygen species
SCFA	short-chain fatty acid
SFA	saturated fat acid
SFB	segmented filamentous bacteria
sICAM-1	intercellular adhesion molecule-1
SINU	Società Italiana di Nutrizione Umana
SPM	specialized pro-resolution mediator
Th	T-helper
TLR	toll-like receptor
TMAO	trimethylamine N-oxide
TNF	tumor necrosis factor
Tregs	regulatory T cells
VCAM	vascular cell adhesion molecule
VDR	vitamin D receptor

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ORCID

Luigi Barrea http://orcid.org/0000-0001-9054-456X
Giovanna Muscogiuri http://orcid.org/0000-0002-8809-4931
Evelyn Frias-Toral http://orcid.org/0000-0002-2228-0141
Daniela Laudisio http://orcid.org/0000-0001-8177-0901
Gabriella Pugliese http://orcid.org/0000-0001-6986-266X
Bianca Castellucci http://orcid.org/0000-0001-9054-456X
Eloisa Garcia-Velasquez http://orcid.org/0000-0002-3211-4307
Silvia Savastano http://orcid.org/0000-0002-3211-4307
Annamaria Colao http://orcid.org/0000-0001-6986-266X

References

Agmon-Levin, N., E. Theodor, R. M. Segal, and Y. Shoenfeld. 2013. Vitamin D in systemic and organ-specific autoimmune diseases. *Clinical Reviews in Allergy & Immunology* 45 (2):256–66. doi: 10.1007/s12016-012-8342-y.

Ajjan, R. A., and A. P. Weetman. 2015. The pathogenesis of Hashimoto's thyroiditis: Further developments in our understanding. *Hormone and Metabolic Research = Hormon- und Stoffwechselforschung = Hormones et Metabolisme* 47 (10):702–10. doi: 10.1055/s-0035-1548832.

Akhmedov, V. A., and O. V. Gaus. 2019. Role of intestinal microbiota in the formation of non-alcoholic fatty liver disease. *Terapevticheskii Arkhiv* 91 (2):143–8. doi: 10.26442/00403660.2019.02.000051.

Altieri, B., L. Barrea, R. Modica, G. Muscogiuri, S. Savastano, A. Colao, and A. Faggiano. 2018. Nutrition and neuroendocrine tumors: An update of the literature. *Reviews in Endocrine & Metabolic Disorders* 19 (2):159–67. doi: 10.1007/s11154-018-9466-z.

Anderson, J. W., P. Baird, R. H. Davis, Jr., S. Ferreri, M. Knudtson, A. Koraym, V. Waters, and C. L. Williams. 2009. Health benefits of dietary fiber. *Nutrition Reviews* 67 (4):188–205. doi: 10.1111/j.1753-4887.2009.00189.x.

Antico, A., M. Tampoia, R. Tozzoli, and N. Bizzaro. 2012. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. *Autoimmunity Reviews* 12 (2):127–36. doi: 10.1016/j.autrev.2012.07.007.

Aparicio-Soto, M., M. Sanchez-Hidalgo, M. A. Rosillo, M. L. Castejon, and C. Alarcon-de-la-Lastra. 2016. Extra virgin olive oil: A key functional food for prevention of immune-inflammatory diseases. *Food & Function* 7 (11):4492–505. doi: 10.1039/c6fo01094f.

Arunachalam, K., H. S. Gill, and R. K. Chandra. 2000. Enhancement of natural immune function by dietary consumption of Bifidobacterium lactis (HN019). *European Journal of Clinical Nutrition* 54 (3):263–7. doi: 10.1038/sj.ejcn.1600938.

Autier, P., P. Mullie, A. Macacu, M. Dragomir, M. Boniol, K. Coppens, C. Pizot, and M. Boniol. 2017. Effect of vitamin D supplementation on non-skeletal disorders: A systematic review of meta-analyses and randomised trials. *The Lancet. Diabetes & Endocrinology* 5 (12):986–1004. doi: 10.1016/S2213-8587(17)30357-1.

Avery, J. C., and P. R. Hoffmann. 2018. Selenium, Selenoproteins, and Immunity. *Nutrients* 10 (9):1203. doi: 10.3390/nu10091203.

Baba, N., S. Samson, R. Bourdet-Sicard, M. Rubio, and M. Sarfati. 2009. Selected commensal-related bacteria and Toll-like receptor 3 agonist combinatorial codes synergistically induce interleukin-12 production by dendritic cells to trigger a T helper type 1 polarizing programme. *Immunology* 128 (1 Suppl):e523–31. doi: 10.1111/j.1365-2567.2008.03022.x.

Babio, N., M. Bullo, J. Basora, M. A. Martinez-Gonzalez, J. Fernandez-Ballart, F. Marquez-Sandoval, C. Molina, J. Salas-Salvado, and P. I. Nureta. 2009. Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. *Nutrition, Metabolism & Cardiovascular Diseases* 19 (8):563–70. doi: 10.1016/j.numecd.2008.10.007.

Back, M., and G. K. Hansson. 2019. Omega-3 fatty acids, cardiovascular risk, and the resolution of inflammation. *FASEB Journal* 33 (2):1536–9. doi: 10.1096/fj.201802445R.

Barrea, L., B. Altieri, B. Polese, B. De Conno, G. Muscogiuri, A. Colao, S. Savastano, Obesity Programs of Nutrition, Education, Research and Assessment (OPERA) Group. 2019. Nutritionist and obesity: Brief overview on efficacy, safety, and drug interactions of the main weight-loss dietary supplements. *International Journal of Obesity Supplements* 9 (1):32–49. doi: 10.1038/s41367-019-0007-3.

Barrea, L., B. Altieri, G. Muscogiuri, D. Laudisio, G. Annunziata, A. Colao, A. Faggiano, and S. Savastano. 2018. Impact of Nutritional Status on Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) Aggressiveness. *Nutrients* 10 (12):1854. doi: 10.3390/nu10121854.

Barrea, L., G. Annunziata, G. Muscogiuri, C. Di Somma, D. Laudisio, M. Maisto, G. de Alteriis, G. C. Tenore, A. Colao, and S. Savastano. 2018. Trimethylamine-N-oxide (TMAO) as novel potential biomarker of early predictors of metabolic syndrome. *Nutrients* 10 (12):1971. doi: 10.3390/nu10121971.

Barrea, L., G. Annunziata, G. Muscogiuri, D. Laudisio, C. Di Somma, M. Maisto, G. C. Tenore, A. Colao, and S. Savastano. 2019. Trimethylamine N-oxide, Mediterranean diet, and nutrition in healthy, normal-weight adults: Also a matter of sex? *Nutrition* 62:7–17. doi: 10.1016/j.nut.2018.11.015.

Barrea, L., A. Arnone, G. Annunziata, G. Muscogiuri, D. Laudisio, C. Salzano, G. Pugliese, A. Colao, and S. Savastano. 2019. Adherence to the Mediterranean diet, dietary patterns and body composition in

women with polycystic ovary syndrome (PCOS). *Nutrients* 11 (10): 2278. doi: 10.3390/nu11102278.

Barrea, L., N. Balato, C. Di Somma, P. E. Macchia, M. Napolitano, M. C. Savanelli, K. Esposito, A. Colao, and S. Savastano. 2015. Nutrition and psoriasis: Is there any association between the severity of the disease and adherence to the Mediterranean diet? *Journal of Translational Medicine* 13 (1):18. doi: 10.1186/s12967-014-0372-1.

Barrea, L., G. Fabbrocini, G. Annunziata, G. Muscogiuri, M. Donnarumma, C. Marasca, A. Colao, and S. Savastano. 2018. Role of nutrition and adherence to the Mediterranean diet in the multidisciplinary approach of hidradenitis suppurativa: Evaluation of nutritional status and its association with severity of disease. *Nutrients* 11 (1):57. doi: 10.3390/nu11010057.

Barrea, L., G. Muscogiuri, G. Annunziata, D. Laudisio, G. de Alteriis, G. C. Tenore, A. Colao, and S. Savastano. 2019. A new light on vitamin D in obesity: A novel association with trimethylamine-N-oxide (TMAO). *Nutrients* 11 (6):1310. doi: 10.3390/nu11061310.

Barrea, L., G. Muscogiuri, G. Annunziata, D. Laudisio, G. Pugliese, C. Salzano, A. Colao, and S. Savastano. 2019. From gut microbiota dysfunction to obesity: Could short-chain fatty acids stop this dangerous course? *Hormones (Athens, Greece)* 18 (3):245–50. doi: 10.1007/s42000-019-00100-0.

Barrea, L., G. Muscogiuri, D. Laudisio, C. Di Somma, C. Salzano, G. Pugliese, G. de Alteriis, A. Colao, and S. Savastano. 2019. Phase angle: A possible biomarker to quantify inflammation in subjects with obesity and 25(OH)D seficiency. *Nutrients* 11 (8):1747. doi: 10.3390/nu11081747.

Barrett, C. W., S. P. Short, and C. S. Williams. 2017. Selenoproteins and oxidative stress-induced inflammatory tumorigenesis in the gut. *Cellular and Molecular Life Sciences: CMLS* 74 (4):607–16. doi: 10.1007/s00018-016-2339-2.

Beharka, A. A., D. Wu, M. Serafini, and S. N. Meydani. 2002. Mechanism of vitamin E inhibition of cyclooxygenase activity in macrophages from old mice: Role of peroxynitrite. *Free Radical Biology & Medicine* 32 (6):503–11. doi: 10.1016/S0891-5849(01)00817-6.

Belkaid, Y., and O. J. Harrison. 2017. Homeostatic immunity and the microbiota. *Immunity* 46 (4):562–76. doi: 10.1016/j.immuni.2017.04.008.

Bera, S., V. De Rosa, W. Rachidi, and A. M. Diamond. 2013. Does a role for selenium in DNA damage repair explain apparent controversies in its use in chemoprevention? *Mutagenesis* 28 (2):127–34. doi: 10.1093/mutage/ges064.

Bergman, P., A. U. Lindh, L. Bjorkhem-Bergman, and J. D. Lindh. 2013. Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 8 (6):e65835. doi: 10.1371/journal.pone.0065835.

Bideci, A., M. O. Camurdan, P. Cinaz, H. Dursun, and F. Demirel. 2005. Serum zinc, insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels in children with type 1 diabetes mellitus. *Journal of Pediatric Endocrinology & Metabolism: JPEM* 18 (10):1007–11. doi: 10.1515/jpem.2005.18.10.1007.

Blackburn, H. 2017. Invited Commentary: 30-year perspective on the seven countries study. *American Journal of Epidemiology* 185 (11): 1143–7. doi: 10.1093/aje/kwx071.

Bobeck, E. A. 2020. Nutrition and Health: Companion Animal Applications: Functional nutrition in livestock and companion animals to modulate the immune response. *Journal of Animal Science* 98 (3):skaa035.

Bonaccio, M., G. Pounis, C. Cerletti, M. B. Donati, L. Iacoviello, G. de Gaetano, and MOLI-SANI Study Investigators. 2017. Mediterranean diet, dietary polyphenols and low grade inflammation: Results from the MOLI-SANI study. *British Journal of Clinical Pharmacology* 83 (1):107–13. doi: 10.1111/bcp.12924.

Bonaventura, P., G. Benedetti, F. Albarede, and P. Miossec. 2015. Zinc and its role in immunity and inflammation. *Autoimmunity Reviews* 14 (4):277–85. doi: 10.1016/j.autrev.2014.11.008.

Bou Ghanem, E. N., S. Clark, X. Du, D. Wu, A. Camilli, J. M. Leong, and S. N. Meydani. 2015. The α-tocopherol form of vitamin E reverses age-associated susceptibility to streptococcus pneumoniae lung infection by modulating pulmonary neutrophil recruitment. *Journal of Immunology (Baltimore, Md.: 1950)* 194 (3):1090–9. doi: 10.4049/jimmunol.1402401.

Boullier, S., M. Tanguy, K. A. Kadaoui, C. Caubet, P. Sansonetti, B. Corthesy, and A. Phalipon. 2009. Secretory IgA-mediated neutralization of Shigella flexneri prevents intestinal tissue destruction by down-regulating inflammatory circuits. *Journal of Immunology (Baltimore, Md.: 1950)* 183 (9):5879–85. doi: 10.4049/jimmunol.0901838.

Bozonet, S. M., A. C. Carr, J. M. Pullar, and M. C. Vissers. 2015. Enhanced human neutrophil vitamin C status, chemotaxis and oxidant generation following dietary supplementation with vitamin C-rich SunGold kiwifruit. *Nutrients* 7 (4):2574–88. doi: 10.3390/nu7042574.

Brandl, K., G. Plitas, C. N. Mihu, C. Ubeda, T. Jia, M. Fleisher, B. Schnabl, R. P. DeMatteo, and E. G. Pamer. 2008. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. *Nature* 455 (7214):804–7. doi: 10.1038/nature07250.

Bscheider, M., and E. C. Butcher. 2016. Vitamin D immunoregulation through dendritic cells. *Immunology* 148 (3):227–36. doi: 10.1111/imm.12610.

Buckland, G., C. A. Gonzalez, A. Agudo, M. Vilardell, A. Berenguer, P. Amiano, E. Ardanaz, L. Arriola, A. Barricarte, M. Basterretxea, et al. 2009. Adherence to the Mediterranean diet and risk of coronary heart disease in the Spanish EPIC Cohort Study. *American Journal of Epidemiology* 170 (12):1518–29. doi: 10.1093/aje/kwp282.

Caballero, S., and E. G. Pamer. 2015. Microbiota-mediated inflammation and antimicrobial defense in the intestine. *Annual Review of Immunology* 33:227–56. doi: 10.1146/annurev-immunol-032713-120238.

Calder, P. C. 2015. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochimica et Biophysica Acta* 1851 (4):469–84. doi: 10.1016/j.bbalip.2014.08.010.

Calder, P. C. 2016. Docosahexaenoic acid. *Annals of Nutrition & Metabolism* 69 (Suppl 1):7–21. doi: 10.1159/000448262.

Calder, P. C. 2017. Omega-3 fatty acids and inflammatory processes: From molecules to man. *Biochemical Society Transactions* 45 (5): 1105–15. doi: 10.1042/BST20160474.

Calder, P. C., N. Ahluwalia, F. Brouns, T. Buetler, K. Clement, K. Cunningham, K. Esposito, L. S. Jonsson, H. Kolb, M. Lansink, et al. 2011. Dietary factors and low-grade inflammation in relation to overweight and obesity. *The British Journal of Nutrition* 106 (Suppl 3):S5–S78. doi: 10.1017/S0007114511005460.

Camargo, A., J. Ruano, J. M. Fernandez, L. D. Parnell, A. Jimenez, M. Santos-Gonzalez, C. Marin, P. Perez-Martinez, M. Uceda, J. Lopez-Miranda, et al. 2010. Gene expression changes in mononuclear cells in patients with metabolic syndrome after acute intake of phenol-rich virgin olive oil. *BMC Genomics* 11:253. doi: 10.1186/1471-2164-11-253.

Cardona, F., C. Andres-Lacueva, S. Tulipani, F. J. Tinahones, and M. I. Queipo-Ortuno. 2013. Benefits of polyphenols on gut microbiota and implications in human health. *The Journal of Nutritional Biochemistry* 24 (8):1415–22. doi: 10.1016/j.jnutbio.2013.05.001.

Cardoso Dal Pont, G., M. Farnell, Y. Farnell, and M. H. Kogut. 2020. Dietary factors as triggers of low-grade chronic intestinal inflammation in poultry. *Microorganisms* 8 (1):139. doi: 10.3390/microorganisms8010139.

Carr, A. C., and S. Maggini. 2017. Vitamin C and immune function. *Nutrients* 9 (11):1211. doi: 10.3390/nu9111211.

Casas, R., E. Sacanella, and R. Estruch. 2014. The immune protective effect of the Mediterranean diet against chronic low-grade inflammatory diseases. *Endocrine, Metabolic & Immune Disorders Drug Targets* 14 (4):245–54. doi: 10.2174/1871530314666140922153350.

Casciato, D. A., L. P. McAdam, J. D. Kopple, R. Bluestone, L. S. Goldberg, P. J. Clements, and D. W. Knutson. 1984. Immunologic abnormalities in hemodialysis patients: Improvement after pyridoxine therapy. *Nephron* 38 (1):9–16. doi: 10.1159/000183270.

Castiglione, D., A. Platania, A. Conti, M. Falla, M. D'Urso, and M. Marranzano. 2018. Dietary micronutrient and mineral intake in the

Mediterranean healthy eating, ageing, and lifestyle (MEAL) study. *Antioxidants (Basel)* 7 (7):79. doi: 10.3390/antiox7070079.

Chandra, R. K. 1997. Nutrition and the immune system: An introduction. *The American Journal of Clinical Nutrition* 66 (2):460S–3S. doi: 10.1093/ajcn/66.2.460S.

Chandra, R. K., G. Heresi, and B. Au. 1980. Serum thymic factor activity in deficiencies of calories, zinc, vitamin A and pyridoxine. *Clinical and Experimental Immunology* 42 (2):332–5.

Chaplin, D. D. 2010. Overview of the immune response. *The Journal of Allergy and Clinical Immunology* 125 (2 Suppl 2):S3–S23. doi: 10.1016/j.jaci.2009.12.980.

Charan, J., J. P. Goyal, D. Saxena, and P. Yadav. 2012. Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis. *Journal of Pharmacology & Pharmacotherapeutics* 3 (4):300–3. doi: 10.4103/0976-500X.103685.

Chassaing, B., L. Etienne-Mesmin, and A. T. Gewirtz. 2014. Microbiota-liver axis in hepatic disease. *Hepatology (Baltimore, Md.)* 59 (1):328–39. doi: 10.1002/hep.26494.

Cheng, C. H., S. J. Chang, B. J. Lee, K. L. Lin, and Y. C. Huang. 2006. Vitamin B6 supplementation increases immune responses in critically ill patients. *European Journal of Clinical Nutrition* 60 (10): 1207–13. doi: 10.1038/sj.ejcn.1602439.

Childs, C. E., P. C. Calder, and E. A. Miles. 2019. Diet and immune function. *Nutrients* 11 (8):1933. doi: 10.3390/nu11081933.

Chinen, T., and A. Y. Rudensky. 2012. The effects of commensal microbiota on immune cell subsets and inflammatory responses. *Immunological Reviews* 245 (1):45–55. doi: 10.1111/j.1600-065X.2011.01083.x.

Cicerale, S., X. A. Conlan, N. W. Barnett, A. J. Sinclair, and R. S. Keast. 2009. Influence of heat on biological activity and concentration of oleocanthal–a natural anti-inflammatory agent in virgin olive oil. *Journal of Agricultural and Food Chemistry* 57 (4):1326–30. doi: 10.1021/jf803154w.

Clark, A., and N. Mach. 2016. Role of vitamin D in the hygiene hypothesis: The interplay between vitamin D, vitamin D receptors, gut microbiota, and immune response. *Frontiers in Immunology* 7: 627.

Colotta, F., B. Jansson, and F. Bonelli. 2017. Modulation of inflammatory and immune responses by vitamin D. *Journal of Autoimmunity* 85:78–97. doi: 10.1016/j.jaut.2017.07.007.

Combs, G. F., Jr., D. N. Midthune, K. Y. Patterson, W. K. Canfield, A. D. Hill, O. A. Levander, P. R. Taylor, J. E. Moler, and B. H. Patterson. 2009. Effects of selenomethionine supplementation on selenium status and thyroid hormone concentrations in healthy adults. *The American Journal of Clinical Nutrition* 89 (6):1808–14. doi: 10.3945/ajcn.2008.27356.

Conlon, M. A., and A. R. Bird. 2014. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 7 (1):17–44. doi: 10.3390/nu7010017.

Cross, D. A., and P. H. Klesius. 1989. Soluble extracts from larval Ostertagia ostertagi modulating immune function. *International Journal for Parasitology* 19 (1):57–61. doi: 10.1016/0020-7519(89)90021-0.

Cunningham-Rundles, S., D. F. McNeeley, and A. Moon. 2005. Mechanisms of nutrient modulation of the immune response. *The Journal of Allergy and Clinical Immunology* 115 (6):1119–28; quiz 1129. doi: 10.1016/j.jaci.2005.04.036.

Cury-Boaventura, M. F., R. Gorjao, T. M. de Lima, J. Fiamoncini, R. P. Torres, J. Mancini-Filho, F. G. Soriano, and R. Curi. 2008. Effect of olive oil-based emulsion on human lymphocyte and neutrophil death. *JPEN: Journal of Parenteral and Enteral Nutrition* 32 (1):81–7. doi: 10.1177/0148607108320181.

Dankers, W., E. M. Colin, J. P. van Hamburg, and E. Lubberts. 2016. Vitamin D in autoimmunity: Molecular mechanisms and therapeutic potential. *Frontiers in Immunology* 7:697.

De Filippis, F., N. Pellegrini, L. Vannini, I. B. Jeffery, A. La Storia, L. Laghi, D. I. Serrazanetti, R. Di Cagno, I. Ferrocino, C. Lazzi, et al. 2016. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut* 65 (11): 1812–21. doi: 10.1136/gutjnl-2015-309957.

De Filippo, C., D. Cavalieri, M. Di Paola, M. Ramazzotti, J. B. Poullet, S. Massart, S. Collini, G. Pieraccini, and P. Lionetti. 2010. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences of the United States of America* 107 (33): 14691–6. doi: 10.1073/pnas.1005963107.

de la Rubia Orti, J. E., M. P. Garcia-Pardo, E. Drehmer, D. Sancho Cantus, M. Julian Rochina, M. A. Aguilar, and I. Hu Yang. 2018. Improvement of main cognitive functions in patients with Alzheimer's disease after treatment with coconut oil enriched Mediterranean diet: A pilot study. *Journal of Alzheimer's Disease: JAD* 65 (2):577–87. doi: 10.3233/JAD-180184.

de Mello, V. D., M. Kolehmainen, U. Schwab, U. Mager, D. E. Laaksonen, L. Pulkkinen, L. Niskanen, H. Gylling, M. Atalay, R. Rauramaa, et al. 2008. Effect of weight loss on cytokine messenger RNA expression in peripheral blood mononuclear cells of obese subjects with the metabolic syndrome. *Metabolism* 57 (2):192–9. doi: 10.1016/j.metabol.2007.08.024.

De Palma, G., I. Nadal, M. C. Collado, and Y. Sanz. 2009. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *The British Journal of Nutrition* 102 (8): 1154–60. doi: 10.1017/S0007114509371767.

Del Chierico, F., P. Vernocchi, B. Dallapiccola, and L. Putignani. 2014. Mediterranean diet and health: Food effects on gut microbiota and disease control. *International Journal of Molecular Sciences* 15 (7): 11678–99. doi: 10.3390/ijms150711678.

Depeint, F., W. R. Bruce, N. Shangari, R. Mehta, and P. J. O'Brien. 2006. Mitochondrial function and toxicity: Role of the B vitamin family on mitochondrial energy metabolism. *Chemico-Biological Interactions* 163 (1–2):94–112. doi: 10.1016/j.cbi.2006.04.014.

Di Daniele, N., A. Noce, M. F. Vidiri, E. Moriconi, G. Marrone, M. Annicchiarico-Petruzzelli, G. D'Urso, M. Tesauro, V. Rovella, and A. De Lorenzo. 2017. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. *Oncotarget* 8 (5):8947–79. doi: 10.18632/oncotarget.13553.

Doan, J. 1977. Specialization of physicians levels and trends in some industrialized countries. *World Health Statistics Report. Rapport de Statistiques Sanitaires Mondiales* 30 (3):207–26.

Dongarra, M. L., V. Rizzello, L. Muccio, W. Fries, A. Cascio, I. Bonaccorsi, and G. Ferlazzo. 2013. Mucosal immunology and probiotics. *Current Allergy and Asthma Reports* 13 (1):19–26. doi: 10.1007/s11882-012-0313-0.

Duan, J., H. Chung, E. Troy, and D. L. Kasper. 2010. Microbial colonization drives expansion of IL-1 receptor 1-expressing and IL-17-producing gamma/delta T cells. *Cell Host & Microbe* 7 (2):140–50. doi: 10.1016/j.chom.2010.01.005.

Dwyer, J. T., P. M. Coates, and M. J. Smith. 2018. Dietary supplements: Regulatory challenges and research resources. *Nutrients* 10 (1):41. doi: 10.3390/nu10010041.

European Food Safety Authority (EFSA). 2002a. Accessed May 15, 2020. http://www.efsa.europa.eu/

European Food Safety Authority (EFSA). 2002b. Summary of dietary reference values. Accessed May 15, 2020. https://www.efsa.europa.eu/sites/default/files/assets/DRV_Summary_tables_jan_17.pdf.

Esposito, K., and D. Giugliano. 2006. Diet and inflammation: A link to metabolic and cardiovascular diseases. *European Heart Journal* 27 (1):15–20. doi: 10.1093/eurheartj/ehi605.

Estruch, R., and M. Camafort. 2015. The Mediterranean diet and plasma lipid profile. *Revista Espanola de Cardiologia (English ed.)* 68 (4):279–81. doi: 10.1016/j.rec.2014.11.021.

Eyerich, K., V. Dimartino, and A. Cavani. 2017. IL-17 and IL-22 in immunity: Driving protection and pathology. *European Journal of Immunology* 47 (4):607–14. doi: 10.1002/eji.201646723.

Fan, Y. Y., N. R. Fuentes, T. Y. Hou, R. Barhoumi, X. C. Li, N. E. P. Deutz, M. Engelen, D. N. McMurray, and R. S. Chapkin. 2018. Remodelling of primary human CD4+ T cell plasma membrane order by n-3 PUFA. *The British Journal of Nutrition* 119 (2):163–75. doi: 10.1017/S0007114517003385.

Fan, Y. Y., L. H. Ly, R. Barhoumi, D. N. McMurray, and R. S. Chapkin. 2004. Dietary docosahexaenoic acid suppresses T cell

protein kinase C theta lipid raft recruitment and IL-2 production. *Journal of Immunology (Baltimore, Md.: 1950)* 173 (10):6151–60. doi: 10.4049/jimmunol.173.10.6151.

Fischer Walker, C., and R. E. Black. 2004. Zinc and the risk for infectious disease. *Annual Review of Nutrition* 24:255–75. doi: 10.1146/annurev.nutr.23.011702.073054.

Fito, M., M. Cladellas, R. de la Torre, J. Marti, D. Munoz, H. Schroder, M. Alcantara, M. Pujadas-Bastardes, J. Marrugat, M. C. Lopez-Sabater, et al. 2008. Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: A randomized, crossover, controlled trial. *European Journal of Clinical Nutrition* 62 (4):570–4. doi: 10.1038/sj.ejcn.1602724.

Fukuda, S., H. Toh, K. Hase, K. Oshima, Y. Nakanishi, K. Yoshimura, T. Tobe, J. M. Clarke, D. L. Topping, T. Suzuki, et al. 2011. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* 469 (7331):543–7. doi: 10.1038/nature09646.

Fung, T. T., M. L. McCullough, P. K. Newby, J. E. Manson, J. B. Meigs, N. Rifai, W. C. Willett, and F. B. Hu. 2005. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *The American Journal of Clinical Nutrition* 82 (1):163–73. doi: 10.1093/ajcn/82.1.163.

Galli, C., and P. C. Calder. 2009. Effects of fat and fatty acid intake on inflammatory and immune responses: A critical review. *Annals of Nutrition & Metabolism* 55 (1–3):123–39. doi: 10.1159/000228999.

Gao, X., Z. Zhang, Y. Li, P. Shen, X. Hu, Y. Cao, and N. Zhang. 2016. Selenium deficiency facilitates inflammation following *S. aureus* infection by regulating TLR2-related pathways in the mouse mammary gland. *Biological Trace Element Research* 172 (2):449–57. doi: 10.1007/s12011-015-0614-y.

Gardener, H., and M. R. Caunca. 2018. Mediterranean diet in preventing neurodegenerative diseases. *Current Nutrition Reports* 7 (1):10–20. doi: 10.1007/s13668-018-0222-5.

Gibbons, R. J. 1977. President-elect's message: "opportunities for dental research". *Journal of Dental Research* 56:D55–62. doi: 10.1177/00220345770560041001.

Gill, S. R., M. Pop, R. T. Deboy, P. B. Eckburg, P. J. Turnbaugh, B. S. Samuel, J. I. Gordon, D. A. Relman, C. M. Fraser-Liggett, and K. E. Nelson. 2006. Metagenomic analysis of the human distal gut microbiome. *Science (New York, N.Y.)* 312 (5778):1355–9. doi: 10.1126/science.1124234.

Gombart, A. F., A. Pierre, and S. Maggini. 2020. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients* 12 (1):236. doi: 10.3390/nu12010236.

Gonzales, R., P. H. Barrett, Jr., L. A. Crane, and J. F. Steiner. 1998. Factors associated with antibiotic use for acute bronchitis. *Journal of General Internal Medicine* 13 (8):541–8. doi: 10.1046/j.1525-1497.1998.00165.x.

Gonzalez, R., I. Ballester, R. Lopez-Posadas, M. D. Suarez, A. Zarzuelo, O. Martinez-Augustin, and F. Sanchez de Medina. 2011. Effects of flavonoids and other polyphenols on inflammation. *Critical Reviews in Food Science and Nutrition* 51 (4):331–62. doi: 10.1080/10408390903584094. [InsertedFromOnline[pubmedMismatch]]

Grubler, M. R., W. Marz, S. Pilz, T. B. Grammer, C. Trummer, C. Mullner, V. Schwetz, M. Pandis, N. Verheyen, A. Tomaschitz, et al. (2017). Vitamin-D concentrations, cardiovascular risk and events: A review of epidemiological evidence. *Reviews in Endocrine and Metabolic Disorders* 18:259–72.

Guillemard, E., F. Tondu, F. Lacoin, and J. Schrezenmeir. 2010. Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. *British Journal of Nutrition* 103 (1):58–68. doi: 10.1017/S0007114509991395.

Gurzell, E. A., H. Teague, M. Harris, J. Clinthorne, S. R. Shaikh, and J. I. Fenton. 2013. DHA-enriched fish oil targets B cell lipid microdomains and enhances ex vivo and in vivo B cell function. *Journal of Leukocyte Biology* 93 (4):463–70. doi: 10.1189/jlb.0812394.

Gutierrez, S., S. L. Svahn, and M. E. Johansson. 2019. Effects of omega-3 fatty acids on immune cells. *International Journal of Molecular Sciences* 20 (3):5028.

Haase, H., and L. Rink. 2009. The immune system and the impact of zinc during aging. *Immunity & Ageing: I & A* 6:9. doi: 10.1186/1742-4933-6-9.

Han, S. N., D. Wu, W. K. Ha, A. Beharka, D. E. Smith, B. S. Bender, and S. N. Meydani. 2000. Vitamin E supplementation increases T helper 1 cytokine production in old mice infected with influenza virus. *Immunology* 100 (4):487–93. doi: 10.1046/j.1365-2567.2000.00070.x.

Hayek, M. G., S. F. Taylor, B. S. Bender, S. N. Han, M. Meydani, D. E. Smith, S. Eghtesada, and S. N. Meydani. 1997. Vitamin E supplementation decreases lung virus titers in mice infected with influenza. *The Journal of Infectious Diseases* 176 (1):273–6. doi: 10.1086/517265.

Hemila, H. 2011. Zinc lozenges may shorten the duration of colds: A systematic review. *Open Respiratory Medicine Journal* 5:51–8.

Hemila, H., and E. Chalker. 2019. Vitamin C can shorten the length of stay in the ICU: A meta-analysis. *Nutrients* 11 (4):708. doi: 10.3390/nu11040708.

Hemila, H., and J. Kaprio. 2011. Subgroup analysis of large trials can guide further research: A case study of vitamin E and pneumonia. *Clinical Epidemiology* 3:51–9.

Hemila, H., J. Virtamo, D. Albanes, and J. Kaprio. 2006. The effect of vitamin E on common cold incidence is modified by age, smoking and residential neighborhood. *Journal of the American College of Nutrition* 25:332–9.

Hill, D. A., M. C. Siracusa, M. C. Abt, B. S. Kim, D. Kobuley, M. Kubo, T. Kambayashi, D. F. Larosa, E. D. Renner, J. S. Orange, et al. 2012. Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation. *Nature Medicine* 18 (4):538–46. doi: 10.1038/nm.2657.

Hoffmann, P. R. 2007. Mechanisms by which selenium influences immune responses. *Archivum Immunologiae et Therapiae Experimentalis* 55 (5):289–97. doi: 10.1007/s00005-007-0036-4.

Hu, S., and M. P. Rayman. 2017. Multiple nutritional factors and the risk of hashimoto's thyroiditis. *Thyroid* 27 (5):597–610. doi: 10.1089/thy.2016.0635.

Huijskens, M. J., M. Walczak, N. Koller, J. J. Briede, B. L. Senden-Gijsbers, M. C. Schnijderberg, G. M. Bos, and W. T. Germeraad. 2014. Technical advance: Ascorbic acid induces development of double-positive T cells from human hematopoietic stem cells in the absence of stromal cells. *Journal of Leukocyte Biology* 96 (6):1165–75. doi: 10.1189/jlb.1TA0214-121RR.

Ideishi, M., M. Sasaguri, M. Ikeda, and K. Arakawa. 1990. Angiotensin-converting activity of tissue kallikrein. *Nephron* 55 (Suppl 1):62–4. doi: 10.1159/000186037.

InterAct, C., D. Romaguera, M. Guevara, T. Norat, C. Langenberg, N. G. Forouhi, S. Sharp, N. Slimani, M. B. Schulze, B. Buijsse, et al. 2011. Mediterranean diet and type 2 diabetes risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study: The InterAct project. *Diabetes Care* 34:1913–8.

Kabat, A. M., N. Srinivasan, and K. J. Maloy. 2014. Modulation of immune development and function by intestinal microbiota. *Trends in Immunology* 35 (11):507–17. doi: 10.1016/j.it.2014.07.010.

Kabelitz, D., and J. Dechanet-Merville. 2015. Editorial: Recent advances in gamma/delta T cell biology: New ligands, new functions, and new translational perspectives. *Frontiers in Immunology* 6:371.

Kahrstrom, C. T., N. Pariente, and U. Weiss. 2016. Intestinal microbiota in health and disease. *Nature* 535 (7610):47. doi: 10.1038/535047a.

Kalina, U., N. Koyama, T. Hosoda, H. Nuernberger, K. Sato, D. Hoelzer, F. Herweck, T. Manigold, M. V. Singer, S. Rossol, et al. 2002. Enhanced production of IL-18 in butyrate-treated intestinal epithelium by stimulation of the proximal promoter region. *European Journal of Immunology* 32 (9):2635–43. doi: 10.1002/1521-4141(200209)32:9<2635::AID-IMMU2635>3.0.CO;2-N.

Kalinski, P. 2012. Regulation of immune responses by prostaglandin E2. *Journal of immunology (Baltimore, Md.: 1950)* 188 (1):21–8. doi: 10.4049/jimmunol.1101029.

Kekkonen, R. A., N. Lummela, H. Karjalainen, S. Latvala, S. Tynkkynen, S. Jarvenpaa, H. Kautiainen, I. Julkunen, H. Vapaatalo,

and R. Korpela. 2008. Probiotic intervention has strain-specific anti-inflammatory effects in healthy adults. *World Journal of Gastroenterology* 14 (13):2029–36. doi: 10.3748/wjg.14.2029.

Kesse-Guyot, E., N. Ahluwalia, C. Lassale, S. Hercberg, L. Fezeu, and D. Lairon. 2013. Adherence to Mediterranean diet reduces the risk of metabolic syndrome: A 6-year prospective study. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD* 23 (7):677–83. doi: 10.1016/j.numecd.2012.02.005.

Kim, M. S., S. S. Hwang, E. J. Park, and J. W. Bae. 2013. Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation. *Environmental Microbiology Reports* 5 (5):765–75. doi: 10.1111/1758-2229.12079.

Kim, W., N. A. Khan, D. N. McMurray, I. A. Prior, N. Wang, and R. S. Chapkin. 2010. Regulatory activity of polyunsaturated fatty acids in T-cell signaling. *Progress in Lipid Research* 49 (3):250–61. doi: 10.1016/j.plipres.2010.01.002.

Kumagai, Y., and S. Akira. 2010. Identification and functions of pattern-recognition receptors. *The Journal of Allergy and Clinical Immunology* 125 (5):985–92. doi: 10.1016/j.jaci.2010.01.058.

La Fata, G., P. Weber, and M. H. Mohajeri. 2018. Probiotics and the gut immune system: Indirect regulation. *Probiotics and Antimicrobial Proteins* 10 (1):11–21. doi: 10.1007/s12602-017-9322-6.

Lacatusu, C. M., E. D. Grigorescu, M. Floria, A. Onofriescu, and B. M. Mihai. 2019. The Mediterranean diet: From an environment-driven food culture to an emerging medical prescription. *International Journal of Environmental Research and Public Health* 16 (6):942.

Laudisio, D., L. Barrea, G. Muscogiuri, G. Annunziata, A. Colao, and S. Savastano. 2020. Breast cancer prevention in premenopausal women: Role of the Mediterranean diet and its components. *Nutrition Research Reviews* 33 (1):19–4. doi: 10.1017/S0954422419000167.

Lee, G. Y., and S. N. Han. 2018. The role of vitamin E in immunity. *Nutrients* 10 (11):1614. doi: 10.3390/nu10111614.

Lee, Y. K., J. S. Menezes, Y. Umesaki, and S. K. Mazmanian. 2011. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences of the United States of America* 108 (Suppl 1): 4615–22. doi: 10.1073/pnas.1000082107.

Leigh, D. A., C. Harris, S. Tait, B. Walsh, and P. Hancock. 1991. Pharmacokinetic study of lomefloxacin and its effect on the faecal flora of volunteers. *The Journal of Antimicrobial Chemotherapy* 27 (5):655–62. doi: 10.1093/jac/27.5.655.

Lemire, J. M., J. S. Adams, R. Sakai, and S. C. Jordan. 1984. 1 alpha,25-dihydroxyvitamin D3 suppresses proliferation and immunoglobulin production by normal human peripheral blood mononuclear cells. *The Journal of Clinical Investigation* 74 (2):657–61. doi: 10.1172/JCI111465.

Li, F., X. Hao, Y. Chen, L. Bai, X. Gao, Z. Lian, H. Wei, R. Sun, and Z. Tian. 2017. The microbiota maintain homeostasis of liver-resident gammadeltaT-17 cells in a lipid antigen/CD1d-dependent manner. *Nature Communications* 8 (1):15265. doi: 10.1038/ncomms15265.

Li, X., X. Bi, S. Wang, Z. Zhang, F. Li, and A. Z. Zhao. 2019. Therapeutic potential of ω-3 polyunsaturated fatty acids in human autoimmune diseases. *Frontiers in Immunology* 10:2241. doi: 10.3389/fimmu.2019.02241.

Lopez-Legarrea, P., N. R. Fuller, M. A. Zulet, J. A. Martinez, and I. D. Caterson. 2014. The influence of Mediterranean, carbohydrate and high protein diets on gut microbiota composition in the treatment of obesity and associated inflammatory state. *Asia Pacific Journal of Clinical Nutrition* 23 (3):360–8. doi: 10.6133/apjcn.2014.23.3.16.

Lordan, R., A. Tsoupras, and I. Zabetakis. 2017. Phospholipids of animal and marine origin: Structure, function, and anti-inflammatory properties. *Molecules* 22 (11):1964.

Loudon, G. H., N. B. Jones, and A. S. Sehmi. 1992. New signal processing techniques for the decomposition of EMG signals. *Medical & Biological Engineering & Computing* 30 (6):591–9. doi: 10.1007/BF02446790.

Lucas, C., N. Barnich, and H. T. T. Nguyen. 2017. Microbiota, inflammation and colorectal cancer. *International Journal of Molecular Sciences* 18 (6):1310.

Mack, D. R. 2005. Probiotics-mixed messages. *Canadian Family Physician* 51 (1455–1457):1462–54.

Macpherson, A. J., and T. Uhr. 2004. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science (New York, N.Y.)* 303 (5664):1662–5. doi: 10.1126/science.1091334.

Maggini, S., A. Pierre, and P. C. Calder. 2018. Immune function and micronutrient requirements change over the life course. *Nutrients* 10 (10):1531. doi: 10.3390/nu10101531.

Maiorino, M. I., G. Bellastella, M. Petrizzo, L. Scappaticcio, D. Giugliano, and K. Esposito. 2016. Mediterranean diet cools down the inflammatory milieu in type 2 diabetes: The MEDITA randomized controlled trial. *Endocrine* 54 (3):634–41. doi: 10.1007/s12020-016-0881-1.

Malaguarnera, L. 2019. Influence of resveratrol on the immune response. *Nutrients* 11 (5):946. doi: 10.3390/nu11050946.

Marik, P. E., and M. Flemmer. 2012. Do dietary supplements have beneficial health effects in industrialized nations: What is the evidence? *JPEN: Journal of Parenteral and Enteral Nutrition* 36 (2): 159–68. doi: 10.1177/0148607111416485.

Marino, R., and M. Misra. 2019. Extra-skeletal effects of vitamin D. *Nutrients* 11 (7):1460. doi: 10.3390/nu11071460.

Marklund, M., J. H. Y. Wu, F. Imamura, L. C. Del Gobbo, A. Fretts, J. de Goede, P. Shi, N. Tintle, M. Wennberg, S. Aslibekyan, et al. 2019. Biomarkers of dietary omega-6 fatty acids and incident cardiovascular disease and mortality. *Circulation* 139 (21):2422–36., doi: 10.1161/CIRCULATIONAHA.118.038908.

Martens, P. J., C. Gysemans, A. Verstuyf, and A. C. Mathieu. 2020. Vitamin D's effect on immune function. *Nutrients* 12 (5):1248. doi: 10.3390/nu12051248.

Martineau, A. R., D. A. Jolliffe, R. L. Hooper, L. Greenberg, J. F. Aloia, P. Bergman, G. Dubnov-Raz, S. Esposito, D. Ganmaa, A. A. Ginde, et al. 2017. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. *BMJ* 356:i6583.

Martinez-Gonzalez, M. A., C. de la Fuente-Arrillaga, J. M. Nunez-Cordoba, F. J. Basterra-Gortari, J. J. Beunza, Z. Vazquez, S. Benito, A. Tortosa, and M. Bes-Rastrollo. 2008. Adherence to Mediterranean diet and risk of developing diabetes: Prospective cohort study. *BMJ* 336 (7657):1348–51. doi: 10.1136/bmj.39561.501007.BE.

Martinez-Gonzalez, M. A., M. Garcia-Lopez, M. Bes-Rastrollo, E. Toledo, E. H. Martinez-Lapiscina, M. Delgado-Rodriguez, Z. Vazquez, S. Benito, and J. J. Beunza. 2011. Mediterranean diet and the incidence of cardiovascular disease: A Spanish cohort. *Nutrition, Metabolism & Cardiovascular Diseases* 21:237–44.

Martins de Lima-Salgado, T., S. Coccuzzo Sampaio, M. F. Cury-Boaventura, and R. Curi. 2011. Modulatory effect of fatty acids on fungicidal activity, respiratory burst and TNF-alpha and IL-6 production in J774 murine macrophages. *The British Journal of Nutrition* 105 (8):1173–9. doi: 10.1017/S0007114510004873.

Maruca, A., R. Catalano, D. Bagetta, F. Mesiti, F. A. Ambrosio, I. Romeo, F. Moraca, R. Rocca, F. Ortuso, A. Artese, et al. 2019. The Mediterranean diet as source of bioactive compounds with multi-targeting anti-cancer profile. *European Journal of Medicinal Chemistry* 181:111579. doi: 10.1016/j.ejmech.2019.111579.

Maywald, M., I. Wessels, and L. Rink. 2017. Zinc signals and immunity. *International Journal of Molecular Sciences* 18 (10):2222.

Mazzocchi, A., L. Leone, C. Agostoni, and I. Pali-Scholl. 2019. The secrets of the Mediterranean diet: Does [only] olive oil matter? *Nutrients* 11 (12):2941. doi: 10.3390/nu11122941.

McDole, J. R., L. W. Wheeler, K. G. McDonald, B. Wang, V. Konjufca, K. A. Knoop, R. D. Newberry, and M. J. Miller. 2012. Goblet cells deliver luminal antigen to CD103+ dendritic cells in the small intestine. *Nature* 483 (7389):345–9. doi: 10.1038/nature10863.

Mena, M. P., E. Sacanella, M. Vazquez-Agell, M. Morales, M. Fito, R. Escoda, M. Serrano-Martinez, J. Salas-Salvado, N. Benages, R. Casas, et al. 2009. Inhibition of circulating immune cell activation: A molecular antiinflammatory effect of the Mediterranean diet. *The American Journal of Clinical Nutrition* 89 (1):248–56. doi: 10.3945/ajcn.2008.26094.

Metherel, A. H., R. J. S. Lacombe, R. Chouinard-Watkins, K. E. Hopperton, and R. P. Bazinet. 2018. Complete assessment of whole-body n-3 and n-6 PUFA synthesis-secretion kinetics and DHA turnover in a rodent model. *Journal of Lipid Research* 59 (2):357–67. doi: 10.1194/jlr.M081380.

Meydani, S. N., L. S. Leka, B. C. Fine, G. E. Dallal, G. T. Keusch, M. F. Singh, and D. H. Hamer. 2004. Vitamin E and respiratory tract infections in elderly nursing home residents: A randomized controlled trial. *JAMA* 292 (7):828–36. doi: 10.1001/jama.292.7.828.

Meydani, S. N., M. Meydani, J. B. Blumberg, L. S. Leka, G. Siber, R. Loszewski, C. Thompson, M. C. Pedrosa, R. D. Diamond, and B. D. Stollar. 1997. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. *JAMA* 277 (17):1380–6. doi: 10.1001/jama.1997.03540410058031.

Milajerdi, A., N. Namazi, B. Larijani, and L. Azadbakht. 2018. The association of dietary quality indices and cancer mortality: A systematic review and meta-analysis of cohort studies. *Nutrition and Cancer* 70 (7):1091–105. doi: 10.1080/01635581.2018.1502331.

Mitchell, W. A., I. Meng, S. A. Nicholson, and R. Aspinall. 2006. Thymic output, ageing and zinc. *Biogerontology* 7 (5–6):461–70. doi: 10.1007/s10522-006-9061-7.

Miyaoka, Y., Y. Kadowaki, S. Ishihara, T. Ose, H. Fukuhara, H. Kazumori, S. Takasawa, H. Okamoto, T. Chiba, and Y. Kinoshita. 2004. Transgenic overexpression of Reg protein caused gastric cell proliferation and differentiation along parietal cell and chief cell lineages. *Oncogene* 23 (20):3572–9. doi: 10.1038/sj.onc.1207333.

Mocchegiani, E., and M. Malavolta. 2004. NK and NKT cell functions in immunosenescence. *Aging Cell* 3 (4):177–84. doi: 10.1111/j.1474-9728.2004.00107.x.

Mullen, A., C. E. Loscher, and H. M. Roche. 2010. Anti-inflammatory effects of EPA and DHA are dependent upon time and dose-response elements associated with LPS stimulation in THP-1-derived macrophages. *The Journal of Nutritional Biochemistry* 21 (5):444–50. doi: 10.1016/j.jnutbio.2009.02.008.

Munoz-Garach, A., C. Diaz-Perdigones, and F. J. Tinahones. 2016. Gut microbiota and type 2 diabetes mellitus. *Endocrinologia y Nutricion* 63 (10):560–8. doi: 10.1016/j.endoen.2016.07.004.

Muscogiuri, G., G. Balercia, L. Barrea, A. Cignarelli, F. Giorgino, J. J. Holst, D. Laudisio, F. Orio, G. Tirabassi, and A. Colao. 2018. Gut: A key player in the pathogenesis of type 2 diabetes? *Critical Reviews in Food Science and Nutrition* 58 (8):1294–309. doi: 10.1080/10408398.2016.1252712.

Muscogiuri, G., L. Barrea, B. Altieri, C. Di Somma, H. P. Bhattoa, D. Laudisio, G. T. Duval, G. Pugliese, C. Annweiler, F. Orio, et al. 2019. Calcium and vitamin D supplementation. Myths and realities with regard to cardiovascular risk. *Current Vascular Pharmacology* 17 (6):610–7. doi: 10.2174/1570161117666190408165805.

Muscogiuri, G., L. Barrea, C. Di Somma, B. Altieri, M. Vecchiarini, F. Orio, T. Spinosa, A. Colao, and S. Savastano. 2019. Patient empowerment and the Mediterranean diet as a possible tool to tackle prediabetes associated with overweight or obesity: A pilot study. *Hormones (Athens, Greece)* 18 (1):75–84. doi: 10.1007/s42000-018-0090-9.

Muscogiuri, G., L. Barrea, D. Laudisio, C. Di Somma, G. Pugliese, C. Salzano, A. Colao, and S. Savastano. 2019. Somatotropic axis and obesity: Is there any role for the Mediterranean diet? *Nutrients* 11 (9):2228. doi: 10.3390/nu11092228.

Nettleford, S. K., and K. S. Prabhu. 2018. Selenium and selenoproteins in gut inflammation: A review. *Antioxidants (Basel)* 7 (3):36. doi: 10.3390/antiox7030036.

Ni, Y. F., J. Wang, X. L. Yan, F. Tian, J. B. Zhao, Y. J. Wang, and T. Jiang. 2010. Histone deacetylase inhibitor, butyrate, attenuates lipopolysaccharide-induced acute lung injury in mice. *Respiratory Research* 11:33. doi: 10.1186/1465-9921-11-33.

Niewiesk, S. 2014. Maternal antibodies: Clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. *Frontiers in Immunology* 5:446.

O'Mahoney, L. L., J. Matu, O. J. Price, K. M. Birch, R. A. Ajjan, D. Farrar, R. Tapp, D. J. West, K. Deighton, and M. D. Campbell. 2018. Omega-3 polyunsaturated fatty acids favourably modulate cardiometabolic biomarkers in type 2 diabetes: A meta-analysis and meta-regression of randomized controlled trials. *Cardiovascular Diabetology* 17 (1):98. doi: 10.1186/s12933-018-0740-x.

Oliviero, F., P. Spinella, U. Fiocco, R. Ramonda, P. Sfriso, and L. Punzi. 2015. How the Mediterranean diet and some of its components modulate inflammatory pathways in arthritis. *Swiss Medical Weekly* 145:w14190. doi: 10.4414/smw.2015.14190.

Ozdal, T., D. A. Sela, J. Xiao, D. Boyacioglu, F. Chen, and E. Capanoglu. 2016. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients* 8 (2):78. doi: 10.3390/nu8020078.

Padovese, R., and R. Curi. 2009. Modulation of rat neutrophil function in vitro by cis- and trans-MUFA. *The British Journal of Nutrition* 101 (9):1351–9. doi: 10.1017/S0007114508076307.

Parikh, M., T. G. Maddaford, J. A. Austria, M. Aliani, T. Netticadan, and G. N. Pierce. 2019. Dietary flaxseed as a strategy for improving human health. *Nutrients* 11 (5):1171. doi: 10.3390/nu11051171.

Parkinson, L., and R. Keast. 2014. Oleocanthal, a phenolic derived from virgin olive oil: A review of the beneficial effects on inflammatory disease. *International Journal of Molecular Sciences* 15 (7):12323–34. doi: 10.3390/ijms150712323.

Parolini, C. 2019. Effects of fish n-3 PUFAs on intestinal microbiota and immune system. *Marine Drugs* 17 (6):374.

Paulos, C. M., C. Wrzesinski, A. Kaiser, C. S. Hinrichs, M. Chieppa, L. Cassard, D. C. Palmer, A. Boni, P. Muranski, Z. Yu, et al. 2007. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8+ T cells via TLR4 signaling. *The Journal of Clinical Investigation* 117 (8):2197–204. doi: 10.1172/JCI32205.

Pauls, S. D., L. A. Rodway, T. Winter, C. G. Taylor, P. Zahradka, and H. M. Aukema. 2018. Anti-inflammatory effects of α-linolenic acid in M1-like macrophages are associated with enhanced production of oxylipins from α-linolenic and linoleic acid. *The Journal of Nutritional Biochemistry* 57:121–9. doi: 10.1016/j.jnutbio.2018.03.020.

Penna, G., and L. Adorini. 2000. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *Journal of Immunology (Baltimore, Md.: 1950)* 164 (5):2405–11. doi: 10.4049/jimmunol.164.5.2405.

Percival, S. S. 1998. Copper and immunity. *The American Journal of Clinical Nutrition* 67 (5 Suppl):1064S–8S. doi: 10.1093/ajcn/67.5.1064S.

Pittler, M. H., and E. Ernst. 2004. Dietary supplements for body-weight reduction: A systematic review. *The American Journal of Clinical Nutrition* 79 (4):529–36. doi: 10.1093/ajcn/79.4.529.

Provvedini, D. M., C. D. Tsoukas, L. J. Deftos, and S. C. Manolagas. 1983. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. *Science (New York, N.Y.)* 221 (4616):1181–3. doi: 10.1126/science.6310748.

Qian, B., S. Shen, J. Zhang, and P. Jing. (2017). Effects of vitamin B6 deficiency on the composition and functional potential of T cell populations. *Journal of Immunology Research* 2017:2197975. doi: 10.1155/2017/2197975.

Queipo-Ortuno, M. I., M. Boto-Ordonez, M. Murri, J. M. Gomez-Zumaquero, M. Clemente-Postigo, R. Estruch, F. Cardona Diaz, C. Andres-Lacueva, and F. J. Tinahones. 2012. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *The American Journal of Clinical Nutrition* 95 (6):1323–34. doi: 10.3945/ajcn.111.027847.

Quigley, E. M. M. 2017. Gut microbiome as a clinical tool in gastrointestinal disease management: Are we there yet? *Nature Reviews. Gastroenterology & Hepatology* 14 (5):315–20. doi: 10.1038/nrgastro.2017.29.

Rejnmark, L., L. S. Bislev, K. D. Cashman, G. Eiriksdottir, M. Gaksch, M. Grubler, G. Grimnes, V. Gudnason, P. Lips, S. Pilz, et al. 2017. Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data. *PLoS One* 12 (7):e0180512. doi: 10.1371/journal.pone.0180512.

Rescigno, M., M. Urbano, B. Valzasina, M. Francolini, G. Rotta, R. Bonasio, F. Granucci, J. P. Kraehenbuhl, and P. Ricciardi-Castagnoli.

2001. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. *Nature Immunology* 2 (4):361–7. doi: 10.1038/86373.

Rigby, W. F., T. Stacy, and M. W. Fanger. 1984. Inhibition of T lymphocyte mitogenesis by 1,25-dihydroxyvitamin D3 (calcitriol). *The Journal of Clinical Investigation* 74 (4):1451–5. doi: 10.1172/JCI111557.

Rooks, M. G., and W. S. Garrett. 2016. Gut microbiota, metabolites and host immunity. *Nature Reviews. Immunology* 16 (6):341–52. doi: 10.1038/nri.2016.42.

Saemann, M. D., G. A. Bohmig, C. H. Osterreicher, H. Burtscher, O. Parolini, C. Diakos, J. Stockl, W. H. Horl, and G. J. Zlabinger. 2000. Anti-inflammatory effects of sodium butyrate on human monocytes: Potent inhibition of IL-12 and up-regulation of IL-10 production. *FASEB Journal* 14 (15):2380–2. doi: 10.1096/fj.00-0359fje.

Sakakeeny, L., R. Roubenoff, M. Obin, J. D. Fontes, E. J. Benjamin, Y. Bujanover, P. F. Jacques, and J. Selhub. 2012. Plasma pyridoxal-5-phosphate is inversely associated with systemic markers of inflammation in a population of U.S. adults. *The Journal of Nutrition* 142 (7):1280–5. doi: 10.3945/jn.111.153056.

Salas-Salvado, J., N. Becerra-Tomas, J. F. Garcia-Gavilan, M. Bullo, and L. Barrubes. 2018. Mediterranean diet and cardiovascular disease prevention: What do we know? *Progress in Cardiovascular Diseases* 61:62–7.

Salas-Salvado, J., M. Bullo, N. Babio, M. A. Martinez-Gonzalez, N. Ibarrola-Jurado, J. Basora, R. Estruch, M. I. Covas, D. Corella, F. Aros, et al. 2018. Erratum. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011;34: 14–19. *Diabetes Care* 41 (10):2259–60. doi: 10.2337/dc18-er10.

Salas-Salvado, J., J. Fernandez-Ballart, E. Ros, M. A. Martinez-Gonzalez, M. Fito, R. Estruch, D. Corella, M. Fiol, E. Gomez-Gracia, F. Aros, et al. 2008. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: One-year results of the PREDIMED randomized trial. *Archives of Internal Medicine* 168 (22):2449–58. doi: 10.1001/archinte.168.22.2449.

Saman, S., W. A. Coetzee, and L. H. Opie. 1988. Inhibition by simulated ischemia or hypoxia of delayed afterdepolarizations provoked by cyclic AMP: Significance for ischemic and reperfusion arrhythmias. *Journal of Molecular and Cellular Cardiology* 20 (2):91–5. doi: 10.1016/s0022-2828(88)80022-1.

Sandhu, K. V., E. Sherwin, H. Schellekens, C. Stanton, T. G. Dinan, and J. F. Cryan. 2017. Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsychiatry. *Translational Research: The Journal of Laboratory and Clinical Medicine* 179:223–44. doi: 10.1016/j.trsl.2016.10.002.

Sandker, G. W., D. Kromhout, C. Aravanis, B. P. Bloemberg, R. P. Mensink, N. Karalias, and M. B. Katan. 1993. Serum cholesteryl ester fatty acids and their relation with serum lipids in elderly men in Crete and The Netherlands. *European Journal of Clinical Nutrition* 47 (3):201–8.

Sandstrom, B., A. Cederblad, B. S. Lindblad, and B. Lonnerdal. 1994. Acrodermatitis enteropathica, zinc metabolism, copper status, and immune function. *Arch Pediatr Adolesc Med* 148:980–5.

Sano, T., W. Huang, J. A. Hall, Y. Yang, A. Chen, S. J. Gavzy, J. Y. Lee, J. W. Ziel, E. R. Miraldi, A. I. Domingos, et al. 2015. An IL-23R/IL-22 circuit regulates epithelial serum amyloid A to promote local effector Th17 responses. *Cell* 163 (2):381–93. doi: 10.1016/j.cell.2015.08.061.

Santos-Marcos, J. A., F. Perez-Jimenez, and A. Camargo. 2019. The role of diet and intestinal microbiota in the development of metabolic syndrome. *The Journal of Nutritional Biochemistry* 70:1–27. doi: 10.1016/j.jnutbio.2019.03.017.

Savanelli, M. C., E. Scarano, G. Muscogiuri, L. Barrea, L. Vuolo, M. Rubino, S. Savastano, A. Colao, and C. Di Somma. 2016. Cardiovascular risk in adult hypopituitaric patients with growth hormone deficiency: Is there a role for vitamin D? *Endocrine* 52 (1): 111–9. doi: 10.1007/s12020-015-0779-3.

Schwager, J., A. Bompard, P. Weber, and D. Raederstorff. 2015. Ascorbic acid modulates cell migration in differentiated HL-60 cells and peripheral blood leukocytes. *Molecular Nutrition & Food Research* 59 (8):1513–23. doi: 10.1002/mnfr.201400893.

Schwingshackl, L., J. Morze, and G. Hoffmann. 2020. Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. *British Journal of Pharmacology* 177 (6):1241–57. doi: 10.1111/bph.14778.

Scotece, M., R. Gomez, J. Conde, V. Lopez, J. J. Gomez-Reino, F. Lago, A. B. Smith III, and O. Gualillo. 2012. Further evidence for the anti-inflammatory activity of oleocanthal: Inhibition of MIP-1α and IL-6 in J774 macrophages and in ATDC5 chondrocytes. *Life Sciences* 91 (23–24):1229–35. doi: 10.1016/j.lfs.2012.09.012.

Sierra, S., F. Lara-Villoslada, M. Comalada, M. Olivares, and J. Xaus. 2006. Dietary fish oil n-3 fatty acids increase regulatory cytokine production and exert anti-inflammatory effects in two murine models of inflammation. *Lipids* 41 (12):1115–25. doi: 10.1007/s11745-006-5061-2.

Singh, N., A. Gurav, S. Sivaprakasam, E. Brady, R. Padia, H. Shi, M. Thangaraju, P. D. Prasad, S. Manicassamy, D. H. Munn, et al. 2014. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 40 (1):128–39. doi: 10.1016/j.immuni.2013.12.007.

Singh, R. K., H. W. Chang, D. Yan, K. M. Lee, D. Ucmak, K. Wong, M. Abrouk, B. Farahnik, M. Nakamura, T. H. Zhu, et al. 2017. Influence of diet on the gut microbiome and implications for human health. *Journal of Translational Medicine* 15 (1):73. doi: 10.1186/s12967-017-1175-y.

Società Italiana di Nutrizione Umana (SINU). 2014a. Accessed May 15, 2020. https://sinu.it/.

Società Italiana di Nutrizione Umana (SINU). 2014b. Accessed May 15, 2020. https://sinu.it/2019/07/09/lipidi/.

Società Italiana di Nutrizione Umana (SINU). 2014c. Accessed May 15, 2020. https://sinu.it/2019/07/09/assunzione-raccomandata-per-la-popolazione-pri-e-assunzione-adeguata-ai/.

Società Italiana di Nutrizione Umana (SINU). 2014d. Accessed May 15, 2020. https://sinu.it/2019/07/09/minerali-assunzione-raccomandata-per-la-popolazione-pri-e-assunzione-adeguataai/.

Slavin, J. 2013. Fiber and prebiotics: Mechanisms and health benefits. *Nutrients* 5 (4):1417–35. doi: 10.3390/nu5041417.

Smith, A. B., 3rd, Q. Han, P. A. Breslin, and G. K. Beauchamp. 2005. Synthesis and assignment of absolute configuration of (-)-oleocanthal: A potent, naturally occurring non-steroidal anti-inflammatory and anti-oxidant agent derived from extra virgin olive oils. *Organic Letters* 7 (22):5075–8. doi: 10.1021/ol052106a.

Soldati, L., L. Di Renzo, E. Jirillo, P. A. Ascierto, F. M. Marincola, and A. De Lorenzo. 2018. The influence of diet on anti-cancer immune responsiveness. *Journal of Translational Medicine* 16 (1):75. doi: 10.1186/s12967-018-1448-0.

Sommer, F., and F. Backhed. 2013. The gut microbiota-masters of host development and physiology. *Nature Reviews. Microbiology* 11 (4): 227–38. doi: 10.1038/nrmicro2974.

Sonnenburg, J. L., and F. Backhed. 2016. Diet-microbiota interactions as moderators of human metabolism. *Nature* 535 (7610):56–64. doi: 10.1038/nature18846.

Spanhaak, S., R. Havenaar, and G. Schaafsma. 1998. The effect of consumption of milk fermented by *Lactobacillus casei* strain Shirota on the intestinal microflora and immune parameters in humans. *European Journal of Clinical Nutrition* 52 (12):899–907. doi: 10.1038/sj.ejcn.1600663.

Sutherland, D. B., K. Suzuki, and S. Fagarasan. 2016. Fostering of advanced mutualism with gut microbiota by immunoglobulin A. *Immunological Reviews* 270 (1):20–31. doi: 10.1111/imr.12384.

Switzer, K. C., Y. Y. Fan, N. Wang, D. N. McMurray, and R. S. Chapkin. 2004. Dietary n-3 polyunsaturated fatty acids promote activation-induced cell death in Th1-polarized murine CD4+ T-cells. *Journal of Lipid Research* 45 (8):1482–92. doi: 10.1194/jlr.M400028-JLR200.

Sypniewska, G. 2007. Pro-inflammatory and prothrombotic factors and metabolic syndrome. *EJIFCC* 18 (1):39–46.

Tamura, J., K. Kubota, H. Murakami, M. Sawamura, T. Matsushima, T. Tamura, T. Saitoh, H. Kurabayshi, and T. Naruse. 1999.

Immunomodulation by vitamin B12: Augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. *Clinical and Experimental Immunology* 116 (1):28–32. doi: 10.1046/j.1365-2249.1999.00870.x.

Tan, J., C. McKenzie, M. Potamitis, A. N. Thorburn, C. R. Mackay, and L. Macia. 2014. The role of short-chain fatty acids in health and disease. *Advances in Immunology* 121:91–119. doi: 10.1016/B978-0-12-800100-4.00003-9.

Tan, T. G., E. Sefik, N. Geva-Zatorsky, L. Kua, D. Naskar, F. Teng, L. Pasman, A. Ortiz-Lopez, R. Jupp, H. J. Wu, et al. 2016. Identifying species of symbiont bacteria from the human gut that, alone, can induce intestinal Th17 cells in mice. *Proceedings of the National Academy of Sciences of the United States of America* 113 (50): E8141–E8150. doi: 10.1073/pnas.1617460113.

Teague, H., M. Harris, J. Fenton, P. Lallemand, B. M. Shewchuk, and S. R. Shaikh. 2014. Eicosapentaenoic and docosahexaenoic acid ethyl esters differentially enhance B-cell activity in murine obesity. *Journal of Lipid Research* 55 (7):1420–33. doi: 10.1194/jlr.M049809.

Terpou, A., A. Papadaki, I. K. Lappa, V. Kachrimanidou, L. A. Bosnea, and N. Kopsahelis. 2019. Probiotics in food systems: Significance and emerging strategies towards improved viability and delivery of enhanced beneficial value. *Nutrients* 11 (7):1591. doi: 10.3390/nu11071591.

The ATBC Cancer Prevention Study Group.1994. The alpha-tocopherol, beta-carotene lung cancer prevention study: Design, methods, participant characteristics, and compliance. *Annals of Epidemiology* 4 (1):1–10. doi: 10.1016/1047-2797(9)90036-1.

Thomas, C. M., and J. Versalovic. 2010. Probiotics-host communication: Modulation of signaling pathways in the intestine. *Gut Microbes* 1 (3):148–63. doi: 10.4161/gmic.1.3.11712.

Thomas, D., and C. Apovian. 2017. Macrophage functions in lean and obese adipose tissue. *Metabolism: clinical and Experimental* 72: 120–43. doi: 10.1016/j.metabol.2017.04.005.

Thorburn, A. N., L. Macia, and C. R. Mackay. 2014. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* 40 (6): 833–42. doi: 10.1016/j.immuni.2014.05.014.

Tilg, H., and A. R. Moschen. 2015. Food, immunity, and the microbiome. *Gastroenterology* 148 (6):1107–19. doi: 10.1053/j.gastro.2014.12.036.

Torres-Fuentes, C., H. Schellekens, T. G. Dinan, and J. F. Cryan. 2017. The microbiota-gut-brain axis in obesity. *The Lancet. Gastroenterology & Hepatology* 2 (10):747–56. doi: 10.1016/S2468-1253(17)30147-4.

Tosti, V., B. Bertozzi, and L. Fontana. 2018. Health benefits of the Mediterranean diet: Metabolic and molecular mechanisms. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 73 (3):318–26. doi: 10.1093/gerona/glx227.

Turchet, P., M. Laurenzano, S. Auboiron, and J. M. Antoine. 2003. Effect of fermented milk containing the probiotic Lactobacillus casei DN-114001 on winter infections in free-living elderly subjects: A randomised, controlled pilot study. *The Journal of Nutrition, Health & Aging* 7 (2):75–7.

Turnbaugh, P. J., F. Backhed, L. Fulton, and J. I. Gordon. 2008. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host & Microbe* 3 (4):213–23. doi: 10.1016/j.chom.2008.02.015.

Vargas, G., J. Azarbal, and R. Tota-Maharaj. 2020. A comparative review of established diets for prevention of cardiovascular disease and newer dietary strategies. *Current Problems in Cardiology* 2020: 100582. doi: 10.1016/j.cpcardiol.2020.100582.

Venter, C., S. Eyerich, T. Sarin, and K. C. Klatt. 2020. Nutrition and the immune system: A complicated tango. *Nutrients* 12 (3):818. doi: 10.3390/nu12030818.

Viaud, S., F. Saccheri, G. Mignot, T. Yamazaki, R. Daillere, D. Hannani, D. P. Enot, C. Pfirschke, C. Engblom, M. J. Pittet, et al. 2013. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science (New York, N.Y.)* 342 (6161): 971–6. doi: 10.1126/science.1240537.

Vieira, S. M., O. E. Pagovich, and M. A. Kriegel. 2014. Diet, microbiota and autoimmune diseases. *Lupus* 23 (6):518–26. doi: 10.1177/0961203313501401.

Wang, J., M. Pae, S. N. Meydani, and D. Wu. 2013. Green tea epigallocatechin-3-gallate modulates differentiation of naïve CD4 T cells into specific lineage effector cells. *Journal of Molecular Medicine (Berlin, Germany)* 91 (4):485–95. doi: 10.1007/s00109-012-0964-2.

Weaver, C. T., C. O. Elson, L. A. Fouser, and J. K. Kolls. 2013. The Th17 pathway and inflammatory diseases of the intestines, lungs, and skin. *Annual Review of Pathology* 8:477–512. doi: 10.1146/annurev-pathol-011110-130318.

Wesemann, D. R., A. J. Portuguese, R. M. Meyers, M. P. Gallagher, K. Cluff-Jones, J. M. Magee, R. A. Panchakshari, S. J. Rodig, T. B. Kepler, and F. W. Alt. 2013. Microbial colonization influences early B-lineage development in the gut lamina propria. *Nature* 501 (7465):112–5. doi: 10.1038/nature12496.

Wessels, I., and L. Rink. 2020. Micronutrients in autoimmune diseases: Possible therapeutic benefits of zinc and vitamin D. *The Journal of Nutritional Biochemistry* 77:108240. doi: 10.1016/j.jnutbio.2019.108240.

Whelan, J., K. M. Gowdy, and S. R. Shaikh. 2016. N-3 polyunsaturated fatty acids modulate B cell activity in pre-clinical models: Implications for the immune response to infections. *European Journal of Pharmacology* 785:10–7. doi: 10.1016/j.ejphar.2015.03.100.

Wiktorowska-Owczarek, A., M. Berezińska, and J. Z. Nowak. 2015. PUFAs: Structures, metabolism and functions. *Advances in Clinical and Experimental Medicine* 24 (6):931–41. doi: 10.17219/acem/31243.

Wong, M. K., A. Darvishzadeh, N. A. Maler, and R. G. Bota. 2016. Dietary supplement nomenclature. *Primary Care Companion for CNS Disorders* 18 (6).

Wrzosek, L., S. Miquel, M. L. Noordine, S. Bouet, M. Joncquel Chevalier-Curt, V. Robert, C. Philippe, C. Bridonneau, C. Cherbuy, C. Robbe-Masselot, et al. 2013. Bacteroides thetaiotaomicron and Faecalibacterium prausnitzii influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent. *BMC Biology* 11:61. doi: 10.1186/1741-7007-11-61.

Wu, C. H., T. C. Huang, and B. F. Lin. 2017. Folate deficiency affects dendritic cell function and subsequent T helper cell differentiation. *The Journal of Nutritional Biochemistry* 41:65–72. doi: 10.1016/j.jnutbio.2016.11.008.

Wu, D., E. D. Lewis, M. Pae, and S. N. Meydani. 2018. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. *Frontiers in Immunology* 9:3160.

Wu, D., and S. N. Meydani. 2008. Age-associated changes in immune and inflammatory responses: Impact of vitamin E intervention. *Journal of Leukocyte Biology* 84 (4):900–14. doi: 10.1189/jlb.0108023.

Wu, Q., M. P. Rayman, H. Lv, L. Schomburg, B. Cui, C. Gao, P. Chen, G. Zhuang, Z. Zhang, X. Peng, et al. 2015. Low population selenium status is associated with increased prevalence of thyroid disease. *Journal of Clinical Endocrinology and Metabolism* 100 (11):4037–47. doi: 10.1210/jc.2015-2222.

Yahfoufi, N., N. Alsadi, M. Jambi, and C. Matar. 2018. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients* 10 (11):1618. doi: 10.3390/nu10111618.

Yakoob, M. Y., E. Theodoratou, A. Jabeen, A. Imdad, T. P. Eisele, J. Ferguson, A. Jhass, I. Rudan, H. Campbell, R. E. Black, et al. 2011. Preventive zinc supplementation in developing countries: Impact on mortality and morbidity due to diarrhea, pneumonia and malaria. *BMC Public Health* 11 (Suppl 3):S23. doi: 10.1186/1471-2458-11-S3-S23.

Yamshchikov, A. V., N. S. Desai, H. M. Blumberg, T. R. Ziegler, and V. Tangpricha. 2009. Vitamin D for treatment and prevention of infectious diseases: A systematic review of randomized controlled trials. *Endocrine Practice* 15 (5):438–49. doi: 10.4158/EP09101.ORR.

Yousefi, B., M. Eslami, A. Ghasemian, P. Kokhaei, A. Salek Farrokhi, and N. Darabi. 2019. Probiotics importance and their immunomodulatory properties. *Journal of Cellular Physiology* 234 (6):8008–18. doi: 10.1002/jcp.27559.

Zhan, W. H. 1989. [Morphology and histology of the placenta from parturients of various nationalities in the Tibet plateau]. *Zhonghua Fu Chan Ke Za Zhi* 24 (341–343):381.

Zhang, Z., X. Gao, Y. Cao, H. Jiang, T. Wang, X. Song, M. Guo, and N. Zhang. 2015. Selenium deficiency facilitates inflammation through the regulation of TLR4 and TLR4-related signaling pathways in the mice uterus. *Inflammation* 38 (3):1347–56. doi: 10.1007/s10753-014-0106-9.

Zhao, Y., S. Joshi-Barve, S. Barve, and L. H. Chen. 2004. Eicosapentaenoic acid prevents LPS-induced TNF-alpha expression by preventing NF-kappaB activation. *Journal of the American College of Nutrition* 23 (1):71–8. doi: 10.1080/07315724.2004.10719345.

Zimmer, J., B. Lange, J. S. Frick, H. Sauer, K. Zimmermann, A. Schwiertz, K. Rusch, S. Klosterhalfen, and P. Enck. 2012. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *European Journal of Clinical Nutrition* 66 (1):53–60. doi: 10.1038/ejcn.2011.141.