

Mediterranean Way of Living as an Optimal Lifestyle and a Dietary Pattern for Healthy Gut and Strong Immunity

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Received: November 05, 2020; Published: December 31, 2020

Abstract

This article reviews the dietary and lifestyle aspects of the Mediterranean way of living and its effects on gut microbiota, immunity and the overall health and well-being. The protective phytochemicals found in mainly plant-based Mediterranean diet viz. vitamins, trace elements such as zinc, selenium, copper and others, omega-3 fatty acids, probiotics, prebiotics and dietary fibers, in addition to the balanced Mediterranean lifestyle, such as conviviality, optimistic mindset, physical activity, adequate rest, and the sense of community, could help in overcoming the current pandemic situation by positively affecting the gut health and boosting the immunity.

Keywords: Mediterranean Diet; Immunity; Anti-Oxidants; Anti-Inflammation; Balanced Gut Microbiota

1. Introduction

A long time ago, Hippocrates said “*All diseases begin in the gut*”. There are many debates if this is true or not, but many experts tend to agree that Hippocrates was right; indeed, *all metabolic diseases are starting in the gut*.

Why is this important in a time of worldwide coronavirus pandemic and several other epidemics in the recent years? It is indeed of vital importance as many people are concerned about staying healthy and maintaining a strong immune system, which could defend the body from viruses, bacteria and other pathogens. More than 70% of the immune system is located in the gut and the gut microbiota is responsible for development and maintaining a healthy immune system. Suppressed immunity and inflammation, which occurs as the immune system’s response to the external invaders (e.g. viruses, bacteria) and subsequent cells’ injuries, have been implicated as causes of many serious diseases. In fact, many chronic metabolic diseases, such as obesity, metabolic syndrome (MS), type 2 diabetes, cardiovascular diseases (CVDs), depression, Alzheimer’s disease (AD) and certain types of cancers start in the gut and further progress as a result of long-term inflammation.

Currently, as the COVID-19 pandemic is happening and there is uncertainty when this pandemic would “end”, strategies to strengthen the gut health have been mainly directed towards a healthy and balanced nutrition that could help boosting the immune system necessary for prevention and management of viral and bacterial infections. These *dietary recommendations* usually involve consumption of mainly plant-based foods, such as foods rich in dietary fibers (vegetables, fruits, grains), proteins (fish, seafood), probiotics (fermented products), healthy fats (fish, seafood) and others. All of them provide diverse nutrients, viz. vitamins A, B6, B12, C, D, E, and folate, trace elements, including zinc, iron, selenium, magnesium, and copper, and omega-3 fatty acids playing important and complementary roles in supporting the immune system. Avoiding ultra-processed food containing refined sugars, salt and unhealthy fats, known to promote inflammatory processes, is also recommended [1-10].

Beside the dietary recommendations, confinement and social distancing have been suggested for reduced spreading of the pandemic. This kind of restrictions significantly modifies the lifestyles of individuals and whole communities. Lack of relationships and social interactions, changes in circadian rhythms, more sedentary lifestyles and other lifestyle restrictions increasing the risks of overweight and obesity, CVDs, and metabolic diseases, are just few of the consequences of the confinement measures. Anxiety, fear, stress, uncertainty for the future and many other issues, whose real health consequences are yet to be determined, are surfacing. Taking all these factors into account, experts are suggesting *lifestyle recommendations*, which could keep the immune system strong. Among them, staying physically active and hydrated, maintaining healthy weight, having adequate rest and night sleep, keeping the stress under control, maintaining the social interactions (remotely) and having optimistic attitude and positive mindset, have been linked to positively affect the gut microbiota, and thus, immunity [11-14].

Looking at the above dietary and lifestyle guidelines for strengthening the immunity, one cannot help but see their resemblance with the “principles” of the traditional Mediterranean way of living.

2. Mediterranean Way of Living

Mediterranean way of living, in general, refers to the traditional Mediterranean diet (MD) and the lifestyle habits and traditions of people living in the Mediterranean basin. It became a part of the UNESCO’s intangible cultural heritage in 2010, where MD is defined as “a set of skills, knowledge, rituals, symbols and traditions concerning crops, harvesting, fishing, animal husbandry, conservation, processing, cooking, and particularly the sharing and consumption of food.”

Mediterranean way of living is often schematically presented as a MD pyramid such as the one proposed by Oldways (Figure 1) [15-18].

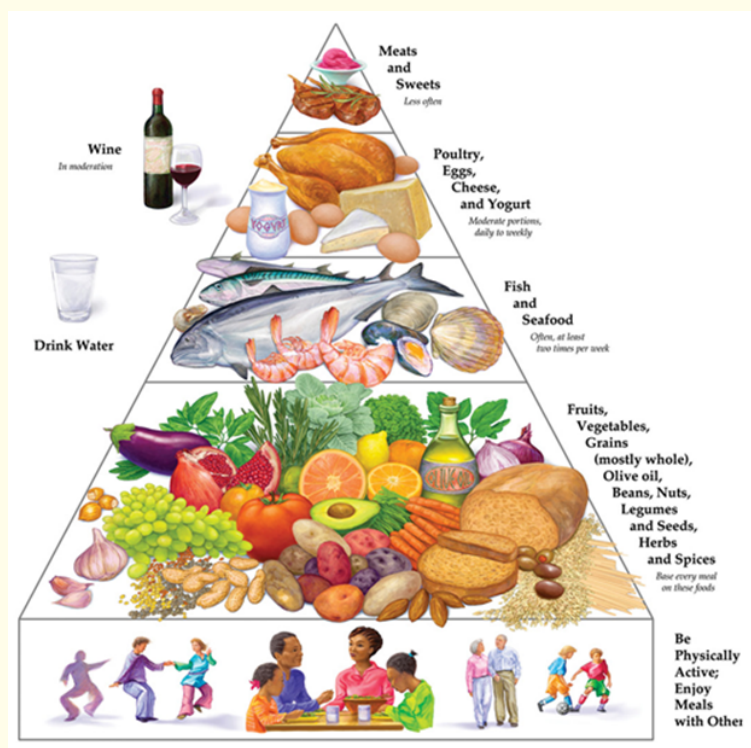


Figure 1: Schematic Presentation of Mediterranean Diet Pyramid (©2009 Oldways Preservation and Exchange Trust; <https://oldwayspt.org/traditional-diets/mediterranean-diet>).

Although it differs from country to country in terms of food choices and cooking practices, religious beliefs and other traditions, MD has a common set of features capturing the dietary and lifestyle habits of the people around the Mediterranean Sea. From a dietary aspect, MD is mostly a plant-based dietary pattern, which emphasizes consumption of fruits, vegetables, whole grains, nuts, legumes and seeds, followed by moderate consumption of fish, poultry, fermented dairy products and extra virgin olive oil (EVOO) as a main source of healthy fats, while the consumption of processed red meat products and products with refined sugars is limited. Plenty of water, fruit juices, herb teas and soups are also frequently consumed, while a moderate amount of red wine is usually taken with the meals. The food preparation and consuming the meals together with family and friends are common habits in the Mediterranean area. Adequate sleep, taking rests during the day, daily physical and leisure activities and being a part of the community are features of the Mediterranean way of living, as well. The socializing aspect and some of the dietary characteristics of MD (e.g. the moderate intake of red wine), have been associated with the longevity and reduced risk of many diseases of the people living in the Mediterranean basin [19-27].

2.1 Dietary Aspects of Mediterranean Way of Living

The MD pyramid (Fig. 1) is organized in a way that the foods consumed daily in abundance are located in the base of the pyramid, followed by those that are moderately consumed, while the food items eaten in limited amounts or occasionally consumed are at the top. MD emphasizes mostly use of plant-derived foods. In particular:

- Daily consumption involves plenty of:
 - Fruits and vegetables,
 - Whole grains, legumes, nuts, and seeds,
 - EVOO,
- Along with a moderate use (several times per week) of:
 - Fermented milk products (sour milk, yogurt, cheese, curds),
 - Fish, poultry, lean red meat, and eggs.
- While limited or occasional use (once-twice a week, or holidays) involves:
 - Refined carbohydrates (sweets, cakes), and
 - Processed red meat products.

Water, no-sugar-added-fruit juices, teas, soups and broths are usually used to keep a good hydration during the day. Moderate red wine consumption with the meals is common in some of the Mediterranean countries depending on the religious beliefs.

Seasonal foods, such as *fruits and vegetables, whole grains, legumes, nuts and seeds* are in the base of the pyramid, meaning their frequent consumption in abundance every day. The complex mixtures of phytochemicals found in the plants, *i.e.* in their roots, seeds, leaves, flowers, and fruits, give them their unique colour, smell, and flavour, as well as dictate their bioactivities and bioavailability within the gut. These phytochemicals have been proven to provide antimicrobial, anti-inflammatory and antioxidant activities in the body. Moreover, the richness of the plants with dietary fibers promotes the feeling of satiety - the feeling of being and staying full for a longer time, which is good for the gut, digestion and maintaining a healthy weight [28-31].

Raw vegetables and fruits, like leafy greens, spinach, chard, cabbage, broccoli, peppers, tomatoes, carrots, olives, onion, garlic, citrus fruits, berries, apples, pomegranate, figs, grapes, pumpkin, squash, watermelon, cantaloupe, and others, are considered as one of the best dietary sources of daily intake of diverse phytonutrients. Consuming variety of “bright colours and textures”, i.e. a rainbow of coloured fresh vegetables and fruits is usually recommended to ensure a broad spectrum of protective phytochemicals. For instance, vegetables are important sources of polyphenolic compounds (e.g. flavonols, flavones, stilbens, etc.), dietary fibers, vitamins A, C, K, E, B6, folate, copper, potassium, magnesium, iron, and choline among many others. The *allium family* of vegetables (garlic, onions, leeks, shallot, scallions, chives), often used as key savory ingredients in MD due to their characteristic culinary flavour are rich in organo-sulphur compounds (e.g. allicin, diallyl disulfide and others) and many powerful antioxidants (quercetin, kaempferol), which reduce the oxidative stress causing cellular damage, as well as are known for their anti-carcinogenic activities. Fruits are rich in dietary fibers, potassium, vitamin C, flavonoids and terpenes. Seasonal fruits are usually used as desserts instead of sweets containing refined carbohydrates. Lean red meat (lamb, pork, beef) is eaten once or few times per week in the traditional MD [31-33].

In the traditional MD, seasonal vegetables and fruits are mostly consumed in the seasons when available, while for the winter months they are usually preserved mainly via fermentation and sun-drying processes. *Fermented vegetables* rich with probiotics, such as cabbage, cauliflower, peppers, cucumbers, carrots, olives and others are often used during off-season, while sun-dried fruits, such as dried figs, dates, apricots, prunes, raisins and others, rich with selenium, copper, potassium, magnesium, B-complex vitamin, vitamin C, carotenoids, and dietary fibers are often used as snacks or for preparation of desserts replacing the sugar.

Whole grains, such as rice, oatmeal and products made of whole grains, viz. breads, pastries, cereals, pasta, crackers and variety of traditional pies filled with cheese, vegetables or fruits, are consumed often during the day. Whole grains are a good source of nutrients, such as dietary fibers, iron, zinc, manganese, folate, magnesium, copper, thiamine, niacin, vitamin B6, phosphorus, selenium, and riboflavin [34].

Protein- and fiber-rich *legumes*, such as different types of beans, peas, lentils, chickpeas and others, are often used in numerous Mediterranean dishes combined together with herbs, spices and vegetables. Other phytonutrients in the legumes are vitamin B6, folate, flavones, phytosterols and various minerals.

Nuts, such as walnuts, almonds, hazelnuts, pistachio, peanuts, pine nuts, cashews, etc. are often used as snacks or as ingredients in the Mediterranean dishes and especially in the desserts. They are good sources of healthy fats (omega-3 fatty acids), proteins, vitamins (tocopherols-vitamin E, vitamin B2, folate), minerals (potassium, copper, phosphorus, selenium, magnesium), phytosterols, fibers and significant loads of antioxidants. Besides the pronounced satiating effect, the nuts' intake usually does not promote obesity and has beneficial effects on metabolic syndrome, diabetes, CVDs and other diseases. Nuts are cholesterol-free and it has been shown that phytosterols in the nuts actually interfere with the cholesterol absorption, and thus, help to lower the blood cholesterol level. Among the nuts, the walnuts have the highest polyphenol content and are often used in the traditional Mediterranean desserts [35-39].

Seeds, such as pumpkin seeds, sunflower seeds, flax seeds, sesame seeds and others, are low-calorie rich sources of proteins, omega-3 fatty acids, fibers, vitamins E and B and minerals (calcium, magnesium, manganese, phosphorus, iron, zinc).

The whole grains, legumes, nuts, seeds, vegetables and fruits provide a plethora of dietary fibers, which are essential nutrients for the gut microbiota and the gut lining, and thus, for the overall health and the protection from external “invaders”.

Spices and herbs, such as rosemary, oregano, black cumin, thyme, ginger, cinnamon, clove, dill, parsley, licorice, as well as garlic and onions are often used in the Mediterranean cuisine as a way to introduce a variety of flavours and palatability to traditional dishes replacing partially the amount of salt. The salt intake is becoming an alarming issue in modern diets as it has been related to hypertension and other heart-related diseases. Herbs and spices are rich sources of micronutrients, antioxidant and anti-inflammatory compounds. Thus,

the addition of selected typical Mediterranean herbs apart from given flavour can contribute to improving the nutritional and especially the antioxidant profile of the dishes. Often the herbs and spices are even used as a natural method to extend the shelf-life of the food [40].

A balanced nutrition of the main meals every day, which includes fruits, vegetables and unrefined whole grain products (breads, oats, cereals and pasta) in combination with legumes, nuts and seeds are complemented with a moderate consumption of *dairy products, fish, and other animal-based foods*. Fish (salmon, tuna, sardines), seafood, poultry, eggs, dairy and fermented dairy products, such as cheese, curds, yogurt, eaten in moderate amounts daily or weekly, are found in the middle portion of the MD pyramid.

Low-fat dairy products and especially fermented milk products, such as cheeses, yogurt, kefir, curd, and other sour milk products, are consumed moderately during the day or week. They are rich in vitamin D, calcium, prebiotics and probiotics, and other nutrients important for the optimal gut, bone and heart health [28,41,42].

Fish and seafood, e.g. sardines, salmon, sea bass, shrimp, tuna, salmon, shellfish and others are considered to be rich in omega-3 long-chain polyunsaturated fatty acids (PUFAs), viz. eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and are consumed moderate-to-often i.e. several times per week. EPA and DHA promote the production of anti-inflammatory compounds important for suppression of chronic inflammation which has been implicated in the etiology of numerous diseases, such as type 2 diabetes, CVD, cancer, obesity, rheumatoid arthritis (RA), neuro-degenerative diseases, etc.

Poultry (e.g. chicken, turkey) and *eggs* are consumed in moderation and are good sources of proteins, vitamins (vitamin D), minerals (zinc, selenium) and healthy fats [28].

Lean red meat (lamb, veal, goat, pork, etc., depending on preference, availability and religious beliefs) is consumed in limited amounts once or few times per week and is usually cooked in small quantities with plenty of vegetables mostly for giving the flavour and rather as a main ingredient of the Mediterranean dishes.

At the top of MD pyramid are processed food products, e.g. sweets, cakes, processed meat products, fast food, carbonated sugary beverages, and others, which are consumed in limited amounts or occasionally (during special occasions and holidays). *Processed foods* (fast food, ready-to-eat frozen food, pizzas, etc.), which are not consumed at all, or consumed in very limited quantities in the traditional MD, usually contain high amounts of refined sugars, salt, emulsifiers and other food additives, unhealthy saturated and trans fats (butter, margarine) – all of them proven to promote inflammatory processes in the body. Moreover, these foods are usually energy-dense giving “immediate” energy boost, but not lasting satiety and contribute to weight gain and development of obesity [43].

The plant origin of the food choices in the MD is found to be responsible for the overall well-being of the people adhering to this diet and their reduced risks for many chronic diseases.

The phytochemicals, viz. polyphenols, carotenoids, tocopherols, tocotrienols, glutathione, vitamins and enzymes, found in the MD, protect the cell damage from oxidative stress. The *oxidative stress* is a result of the generation of oxidative species (free radicals, reactive oxygen and reactive nitrogen species) in the body, which is usually triggered by unhealthy diets and external factors, such as smoke, pollution, chemicals, drugs, UV rays, etc. The oxidative stress causes structural and functional damages of the main biomolecules in the body, such as DNA, lipids, and proteins and has been implicated in the pathogenesis of many chronic degenerative diseases, inflammation, neuro-degenerative disorders and aging processes. In particular, the imbalance between the production of oxidative species in the body and the antioxidant defense could lead to many pathological situations (i.e. diseases). To counteract this oxidative stress caused by the reactive species, the body needs various types of antioxidants. The body fights with its own antioxidative defense mechanism, but *de novo* antioxidants' production in the human cells is limited. Therefore, the body needs a continuous supply of external antioxidants, which to ensure better health is preferred to come from the diet as dietary antioxidants. The traditional MD is rich in antioxidants, such

as vitamins (β -carotene, vitamin C, and vitamin E), natural folate, polyphenols (flavonoids), carotenoids, and selenium. Many of the MD food phytochemicals are also anti-inflammatory in nature, and thus, do not support the generation of pro-inflammatory molecules in the body [31,33].

The hallmark of MD, *extra virgin olive oil* (EVOO), is a main source of dietary lipids in the traditional MD. Its unique composition, the fatty acid composition and the richness with bioavailable polyphenols, is responsible for the health protective benefits of EVOO and its resistance to elevated temperatures, which makes it good for both, cooking and salad dressings. EVOO as one of the most studied oils to-date has been associated with extended life expectancy and reduction of the risks of many age-related degenerative diseases. Reduction of the oxidative stress and suppression of chronic inflammation have been associated with EVOO in relation to the modulation of the aging processes and promotion of healthy aging. Moreover, EVOO has been reported to be inversely associated with the risks for several cancers and CVDs, as well as to positively affect the blood lipids, i.e. cholesterol and triglyceride levels. All these benefits are due to the richness of the EVOO with valuable bioavailable phytochemicals, such as the optimal fatty acid profile, especially monounsaturated fatty acids (MUFA) viz. oleic, palmitic, linoleic, and α -linoleic acid, tocopherols (vitamin E), beta-carotene and a variety of polyphenols. Diversity of the polyphenols, such as phenolic acids (caffeic, p-cumaric, ferulic acid), phenolic alcohols (hydroxytyrosol, tyrosol), secoiridoids (oleuropein), flavonoids (quercetin, luteolin, apigenin), lignans and others, result in a strong antioxidative activity of EVOO, capable to scavenge oxidative species, increase cellular endogenous antioxidant defenses, and thus, reduce the oxidative stress in the body. For instance, hydroxytyrosol and tyrosol, which comprise over 90% of the total phenolic content of EVOO, have been proven for their very high rates of absorption in humans upon ingestion (40-95% depending on the EVOO quality), while oleuropein in EVOO has been shown to have superior anti-oxidation effects on blood lipids when compared with other cooking oils with similar fatty acid content. Moreover, the EVOO's phytochemicals decrease the inflammation via modulation of pro-inflammatory cytokines and enhance the immune function in the body, as well as act toward enhanced fat metabolism and enhanced energy expenditure [26,43-52].

Hydration is an important factor for an optimal health. Daily intake of plenty of water, non-sugary drinks (juices, herbal teas), fermented drinks (yogurt), coffee, broths and different soups, are frequently consumed in the traditional MD during the day [53-55]. Often consumption of wine with the meals, but in moderation, is a common practice used in parts of the Mediterranean area and proven to have positive effects on health and longevity due to its polyphenol (resveratrol) content [56-59].

Representative food produces often used in the MD along their phytonutrients are given in figure 2.

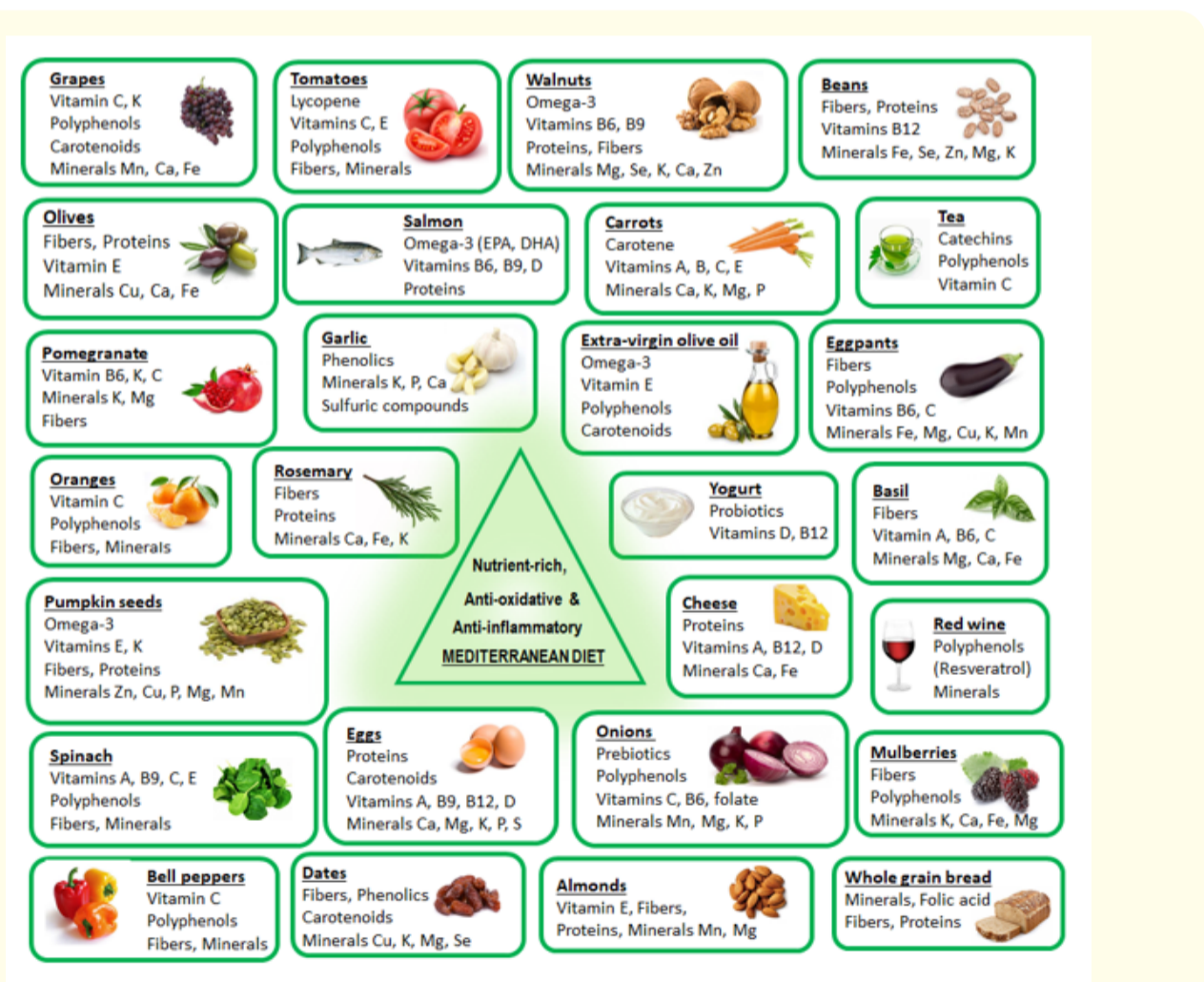


Figure 2: Selected Typical Foods in the Mediterranean Diet with Their Nutrients (MD Inspired™).

2.2 Socio-Cultural, Economic and Ecological Aspects of the Mediterranean Way of Living

Besides the plant-based diet, Mediterranean way of living constitutes a set of *lifestyle habits and behaviors*, which have been associated with a better cognitive performance, well-being and overall health of the people adhering to this lifestyle. In particular, the social interactions, the social support and the sense of community, the group participation in leisure and physical activities, and the adequate rest and sleep patterns have been proven to have positive effects on the cognitive functions [60-66].

The socializing aspect of the MD, i.e. the *conviviality* (con-viv-i-al-i-ty = the quality of being friendly and lively; friendliness) is an important component of the Mediterranean way of living adding the social and cultural values to the traditional meals, beyond their nutritional values. The social support and interactions, enjoying life events together with family and friends, sitting around the table and sharing the food, having lengthy meals with others and mealtime conversations, as well as post-lunch rests (known as *siestas*, naps) are common practices in the traditional Mediterranean lifestyle. In the past, the mealtimes have been even considered as opportunities for social interactions and have been used to keep families and communities together.

Cooking is also an important and enjoyable activity for the people in the Mediterranean area. It is considered as a relaxing and fun activity, which is usually done together with family members and friends. The pleasure associated with the conviviality of meals seems to positively affect food behaviors and the health status of the people, who have been associated with lower risk of CVDs, lower cancer incidence, improved overall mortality and increased longevity, as well as gives a *sense of "belongingness"*. *Cooking practices* are usually minimal, i.e. done in a way that does not destroy the nutritional profile of the used ingredients. Traditionally, in the Mediterranean cuisine, the vegetables along with herbs and spices are cooked in EVOO. EVOO acts as an active medium that extracts the nutrients from the cooked vegetables into the oil phase of the dish and makes them more bioavailable and bio-accessible for the human body. On the other hand, the phytonutrients from the cooked vegetables in EVOO further stabilize the oil at higher temperature, and thus, prevent the formation of trans-fats and other harmful products during food cooking in EVOO, which is the case with other cooking oils. For instance, onions and garlic cooked in EVOO are the base for many sauces and Mediterranean dishes, where the preparation process actually amplifies the nutritional value (especially the antioxidant capacity) of the sauce or the dish compared to that of the raw ingredients. The typical Mediterranean dish, *tomato sofrito*, for example, is rich with bioavailable lycopene, which is transformed from its natural form in the tomato by the specific cooking procedure in EVOO and the presence of onions, garlic, and herbs [67-71].

MD also emphasizes the use of foods which are *seasonal and locally-sourced*. Harvesting ripe fruits and vegetables, short post-harvest handling, storage and transportation play important roles in preserving food phytonutrients. The preference for fresh and minimally processed foods actually maximize the content of protective nutrients in the diet due to the minimal nutrient loss usually occurring during cooking. Using seasonal, local and biodiverse products whenever possible is seemingly good not only for the health and well-being, but for the overall inclusion of the people and strengthening the sense of community. Originally as a diet of poor men, the food in the traditional MD is *eaten in moderation* and portion sizes have been, in general, based on frugality. Unfortunately, the Western diets' influences, modernization and globalization have greatly affected the seasonality and the moderation aspects of the Mediterranean way of living in the recent years.

Regularly having a moderate *physical activity* such as, daily walks as a basic complementary activity to the diet is beneficial for balancing the energy intake, for healthy body weight maintenance and for many other health benefits. In fact, the MD has evolved over centuries as a diet of mostly "poor" people in the Mediterranean area working hard to produce food in mainly bad terrains for survival. Such hard work included a lot of physical activity with the crops in the fields and taking care of the farm animals [72-76]. Therefore, the physical activity in combination with moderate portions of foods with different nutrients could yield *healthy weight* in people adhering to MD [77-79].

Leisure activities mainly done outdoors (e.g. gardening, fishing, knitting, chess and other games) and enjoying them in a company with others make these activities more enjoyable and strengthen the sense of community. *Resting* is also a part of a healthy and balanced Medi-

terranean lifestyle. An adequate night sleep, as well as resting during the day (nap, *siesta*, if possible) is also a part of a balanced traditional Mediterranean lifestyle [63-66].

Overall, the nutritional value of the MD along with its associated social lifestyle aspects add to a better management of stresses, reducing the sense of loneliness and isolation, and increasing the sense of self-worth and the sense of contributing to the community; all together positively affecting the health, mood and cognitive functions.

2.3. Health benefits of Mediterranean Way of Living

The health benefits of people adhering to the traditional Mediterranean diet were first reported in the Seven Countries Study by Dr. Keys. Originally, MD was linked to significantly reduced rates of CVDs observed among the people residing in the Mediterranean region, but over the years MD has been also linked to reduced rates of many other chronic diseases, viz. several types of cancers [80-86], MS [86-89], obesity [83], diabetes [90-93], atherosclerosis [94], cognitive impairment [95-100], depression [101-104], CVD [105-112] and other neuro-degenerative disorders (AD, Parkinson’s Disease, PD) [113-115], as well as higher life expectancy in the Mediterranean populations compared to other populations [116-131].

Figure 3 summarizes the most important phytochemicals found in the traditional MD, its protective effects against multiple diseases, and the benefits that people enjoy by adhering to this diet.

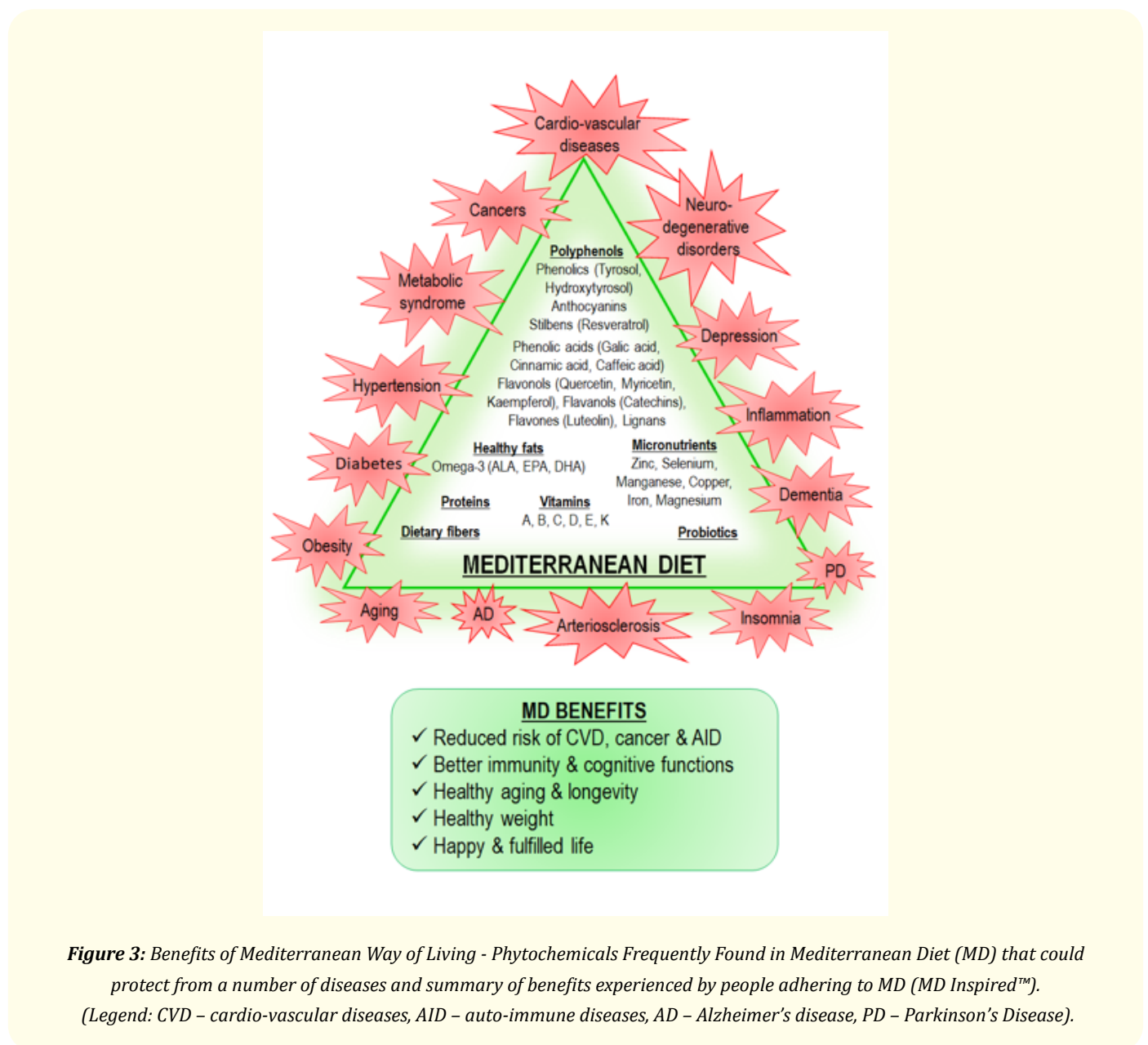


Figure 3: Benefits of Mediterranean Way of Living - Phytochemicals Frequently Found in Mediterranean Diet (MD) that could protect from a number of diseases and summary of benefits experienced by people adhering to MD (MD Inspired™). (Legend: CVD – cardio-vascular diseases, AID – auto-immune diseases, AD – Alzheimer’s disease, PD – Parkinson’s Disease).

Figure 3 Benefits of Mediterranean way of living - phytochemicals frequently found in Mediterranean diet (MD) that could protect from a number of diseases and summary of benefits experienced by people adhering to MD. (Legend: CVD - cardio-vascular diseases, AID - auto-immune diseases, AD - Alzheimer's disease, PD - Parkinson's Disease).

The health benefits of MD have been mainly associated to the high intake of unprocessed nutrient-rich plant-based foods. In particular, the crucial dietary components of MD believed to be responsible for its health benefits are:

- Long-chain omega-3 fatty acids originating mainly from fresh fish, EVOO, nuts, and seeds.
- Variety of powerful antioxidants, especially polyphenols (quercetin, resveratrol, hydroxytyrosol) originating from vegetables, fruits, EVOO, red wine, tea, etc.
- Probiotics originating from fermented milk products (yogurt, sour curds, cheeses) and fermented vegetables.
- Vitamins (A, D, E, C, B6, B9, B12), minerals (zinc, iron, selenium, magnesium, manganese) and other phytonutrients (carotenoids-lycopene) having strong antioxidant and anti-inflammatory activities originating from vegetables, fruits, herbs and spices.

Recently, two studies have linked the protective effects of the MD with its positive changes on the gut microbiota; in particular, participants adhering to the MD were found to have richer populations of beneficial bacteria and reduced pathogenic bacteria in their guts compared to the controls [132,133].

3. Mediterranean Way of Living for a Healthy Gut

3.1. A Diverse Gut is a Healthy Gut

The human gut microbial communities are a mixture of different microorganisms collectively called the gut microbiota or "gut flora". The gut is comparable to an organ, because it contributes directly and/or indirectly in various vital physiological functions necessary for survival. Some of these functions include immunity, metabolism, fertility, development, aging and antioxidant activities, which promote health and fitness.

A rich and diverse microbial community results in a balanced and healthy gut microbiota composition leading to an optimal host's health and well-being. This state of a healthy and balanced microbiota ecosystem, called *eubiosis*, is essential for proper metabolism of different dietary components, extraction of the nutrients and their supply to the body. The microbiota ecosystem starts developing from early stages of life, with the baby's delivery and feeding practices, and is changing throughout the life depending on the lifestyle and habits, the environment, the antibiotics (and other drugs) use, and mostly by the nutrition choices [134-138].

Disruption and imbalance of the microbiota, known as *dysbiosis*, in most cases is characterized as a pathogenic state of the gut or gut with diminished microbiota. It usually happens via a loss of beneficial bacteria, overgrowth of harmful bacteria, and/or loss of the microbial diversity in the gut. In any case, it has been implicated as origin of many conditions and diseases, including MS [139], CVD [140,141], obesity [142], auto-immune diseases (AID) [143], inflammatory bowel diseases (IBD) [144-146] and certain types of cancers [147]. The bidirectional communication between the gut microbiota and the brain, well-known as the *gut-brain axis*, have been shown to play a key role also in several neurological disorders, such as depression, AD, PD, autism spectrum disorders and others [148-163].

The gut-brain axis is a complex communication system, which among others include the immune system. The immune system protects the body by using its *innate and adaptive immune systems*. More specifically, the innate immune system is comprising the physical barriers (skin, epithelial lining in gastrointestinal tract and respiratory tract) and the biochemical barriers (secretions and mucus), while the adaptive immune system consists of numerous different immune cells and antibodies. Depending on the nature of the insult (pathogen),

certain levels of defense are triggered, and in general, the innate immune system is activated first. If the pathogen manages to avoid the innate defenses, then the more complex, adaptive response is triggered, which produce antibodies to target and destroy the pathogen. The gut-brain communication is influenced by the composition and diversity of the gut microbiota, hormones and immune- and neuro-peptides produced in the gut, but also by the integrity of the intestinal wall serving as the physical barrier to the external environment. The integrity of this intestinal wall as a part of the gut mucosa is a functional barrier which controls the transfer of the nutrients through the intestinal wall into the bloodstream and defending the body from the penetration of unwanted dangerous molecules. Furthermore, the gut mucosa is a multi-layered system consisting of an external “anatomical” barrier and an inner “functional” immunological barrier. This deeper, inner barrier, consists of a complex network of immune cells, which could contain up to 70% of the body’s total number of immunocytes, thus it is involved in the body’s response to the attack of pathogens (viruses and bacteria). Therefore, keeping the integrity of the barrier walls and the gut mucosa intact is crucial for the health [135,147,160-163].

If the integrity of the gut mucosa is impaired by a poor diet and/or other external insults, a condition known as a “leaky” gut will allow passage of undigested food particles, toxic waste, and harmful bacteria into the blood circulation, and thus, could affect the physiological, behavioral, cognitive, and memory functions of the brain, contributing to chronic diseases, mental health conditions and neuropsychiatric disorders. For example, intestinal dysbiosis and mucosal surfaces with impaired microbiota function and diversity have been related to the pathogenesis of several AIDs.

Furthermore, a close relationship between inflammation and suppressed immunity for various inflammation-caused diseases has been established. Maintaining a strong immune system could lead to reduced inflammation in the body, and thus, reduced risk of these diseases. *Inflammation* is a biological response of the immune system to events triggered by a variety of factors, including pathogens (viruses, bacteria), damaged cells, ionized pollution, toxic compounds, smoke, alcohol, etc. Like the oxidative stress, and sometimes caused by it, inflammation is a major factor in the pathology of many chronic diseases including CVD, cancer [147], type 2 diabetes, MS, AD [164] and obesity [165,166], among others. Several immune-mediated inflammatory diseases, such as RA, IBD [144], multiple sclerosis, systemic lupus erythematosus, and psoriasis have been determined to originate from suppressed immunity [152,164-167].

3.2. Dietary Effects on Gut Microbiota

Multiple factors have effects on the gut microbiota. The diet and nutrition have been recognized among the major factors affecting the composition (diversity and richness), stability and functioning of the gut microbes [168,169]. The right microbial species in the gut are critical, because they metabolize the food and extract its nutrients. The gut microbiota health, thus, is affecting the production of beneficial and harmful metabolites, which are responsible for the host health or incidence and progression of metabolic diseases. Metabolites derived from both the digestion and microbial fermentation of dietary and nutritional components have a significant effect on many organs including the brain, and the host immune responses [170-190].

“Poor” nutrition via the gut microbiota plays a crucial role in immunity-related diseases, cardiometabolic conditions and diet-related cancers, among others. Nutrition-related chronic diseases represent a global problem, and the effects are not restricted to particular population groups or particular countries. The first two years of life is a critical period for overall development including the gut microbiota, which further change with age. Therefore, early life exposures to poor nutrition may affect the children for long-term health effects including obesity, metabolic conditions, and CVDs; all combined are responsible for the most deaths globally. The prevalence of these diseases is rapidly increasing, and evidence shows that diet and lifestyle are key areas of intervention to decrease their burden on every society [190].

Dietary patterns rich in fresh produce, including a variety of vegetables, fruits and whole grains, have been proven to promote *eubiosis*. The food-derived bioactive compounds, the phytochemicals, contribute by means of their interactions with the gut microbiota. High fruit and vegetable intakes rich in dietary fibers, improve the cognitive functions, as well as reduce the risk of developing neurodegenerative processes, such as dementia, via the bidirectional gut-brain axis.

It is known that the human enzymes are not able to digest most complex carbohydrates of the *dietary fibers*, but instead these polysaccharides are metabolized by the gut microbes, which generate short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. Acetate, propionate and butyrate are actually produced by certain classes of beneficial bacteria amongst which are *Bacteroides*, *Bifidobacterium*, *Clostridium* and *Eubacterium Lactobacillus* and are playing roles in different relationships of the gut with other organs in the body. For instance, butyrate serves as an energy substrate for colonocytes, but also inhibits inflammation; propionate is mostly absorbed by the liver, inhibits inflammation, as well as improves the insulin sensitivity, while the acetate is mostly released into circulation to reach peripheral tissues and organs, including the brain. Both propionate and acetate have been found to increase *satiety*, while acetate and butyrate have positive effects on some neurological disorders [191,192].

Diets low in dietary fibers may irreversibly reduce microbial diversity and lead to the disappearance of specific bacterial species in the digestive system. Accordingly, the low intake of dietary fibers and the increased amounts of unhealthy fats and refined sugar, typical for the Western diets, may contribute to depletion of specific bacterial taxa. These alterations may result in dysfunctions and *dysbiosis*, contributing to increase in the development of chronic inflammatory diseases, such as IBD, colorectal cancer, allergies, AIDs, obesity and its associated pathologies [191-197].

Thousands of *polyphenolic compounds* have been found in various plants and plant-derived foods, such as fruits, vegetables, tea, herbs, seeds, grains, coffee, tea, cocoa, and wine. Polyphenols can alter the gut microbiota, resulting in a greater abundance of beneficial microbes. For instance, the anthocyanins significantly stimulate the growth of beneficial members of the gut microbial community (*Bifidobacterium spp.*, *Lactobacillus* and *Enterococcus spp.*). Pro-anthocyanidins, present in grapes, apples, cocoa, red wine, berries, and some nuts, exert local beneficial biological actions on colonic epithelial cells, resulting in protective effects against inflammation-mediated diseases including colorectal cancer. Quercetin alters the composition of gut microbiota and inhibits the growth of bacterial species associated with diet-induced obesity. Also, some phenolic compounds could exert prebiotic activity, thus having inhibitory effects on pathogenic bacteria. Gut microbiota in turn can modulate the transformation of phenolic compounds into smaller metabolites, and therefore, can positively influence their bioavailability in the body [198-203].

Prebiotics defined as “selectively fermented ingredients that result in specific changes, in the composition and/or activity of the gastrointestinal microbiota, and therefore, conferring benefits upon host health” are non-digestible food ingredients in dietary fibers that nourish and selectively stimulate the growth and/or inhibition of specific colonic bacteria. Culinary spices including black pepper, cayenne pepper, cinnamon, ginger, oregano, rosemary and turmeric, among others, have been shown to have prebiotic effects inducing positive changes in human gut microbiota [192,195,204, 205].

Probiotics, valuable dietary components, found in fermented dairy and non-dairy products, can markedly modulate the gut microbiota and their functions. In particular, they can enhance the systematic immunity, which further reduces the chances of allergy and inflammation by immunomodulation. Probiotic foods have been found to have a positive effect on anxiety. In the present time of feeling anxious about the current pandemic and the uncertain future, consuming probiotic-rich food might help with the anxiety [206-216].

A study measuring the stress hormone cortisol levels as a mean to assess the emotional processing of the participants by taking prebiotic fibers showed increased attentional vigilance to positive versus negative stimuli. Therefore, the ingestion of prebiotics and probiotics is able to impose mental health benefits through interactions with commensal gut bacteria; such components are known as “*psychobiotics*” [217-220].

Vitamins and minerals play a key role in regulating energy metabolism and immune functions among other benefits. Vitamins A, B6, B12, C, D, E and folate, and trace elements, including zinc, iron, selenium, magnesium, and copper, play important and complementary roles in supporting the immune system. Their deficiencies are known to decrease the host resistance to infections [221-223].

Vitamin C, in particular, supports the epithelial barrier function, the growth and function of the immune cells, the white blood cell migration to sites of infection and the antibody production, among other effects. People deficient in vitamin C are susceptible to severe respiratory infections, such as pneumonia [221].

Vitamin D also prevents respiratory infections through several immunoregulatory functions including the decreased production of pro-inflammatory cytokines by the innate immune system, therefore reducing the risk of asthma, allergic diseases and pneumonia. It profoundly affects the immunity, because many immune cells have vitamin D receptors that affect their function after the ligand binding. Moreover, vitamin D regulates the production of specific antimicrobial proteins that directly kill pathogens, and thus helps to reduce the risks of infections. Its effect on the gut microbiome is mainly by increasing the abundance of potentially beneficial bacterial strains and therefore, having long-term implications on the immune system modulation [221,224, 225].

Other antioxidant vitamins, such as carotenoids influence the gut microbiota composition, and vice versa, the anti-inflammatory effects of *beta-carotene* are mediated by the gut microbiota [226]. *Vitamin E* is found to reduce the risk of upper respiratory tract infections, but not lower respiratory tract infections. Vitamin *B6, B12 and folate* play role in strengthening the immunity and are found to be complementary to the minerals with effects on immunity [221].

Minerals are also involved in numerous bacterial physiological processes impacting the gut microbiota. For instance, *dietary zinc* regulates the gut epithelial wall and effectively counteracts some of the pathogenic bacteria (e.g. *Clostridium difficile* which is causing the life-treating inflammation of the colon). It is actually helping in maintaining and development of the cells in both the innate and adaptive immune systems [222,223,227]. *Iron* influences the gut composition, and is another key element involved as a cofactor in iron-containing proteins for redox reactions and metabolic pathways [228-230]. Selenium, copper and magnesium are also complementary to vitamins and other minerals in the support of healthy gut and strong immunity [222,228-230].

Inflammation is a key component of the immune response. *Omega-3 fatty acids*, especially EPA and DHA, support the immune system, and more specifically help the anti-inflammatory responses. Their deficiency means delayed resolution of the inflammation. In situations of bacterial and viral infections, like the current COVID-19 causing uncontrolled inflammation and acute respiratory distress syndrome (ARDS), EPA and DHA are beneficial as they have shown protective effects in animal models against acute lung injuries and ARDS [231-234].

Hydration is another important factor for keeping strong immunity. The immune system is dependent on the nutrients to be delivered by the blood stream, which is mostly made of water. Without supply of sufficient amount of water, the transport of nutrients to the organs will be affected. Also, hydration is important for detoxification – it helps the body to naturally eliminate toxins and pathogens by e.g. increasing lymphatic draining.

3.3. Non-dietary Effects on Gut Microbiota

Besides the nutrition, age and genetics, the lifestyle factors, viz. stress, smoking, physical activity, sleep, drugs (antibiotics, recreational drugs) etc., circadian rhythm disruptions, environmental pollution (toxins, pesticides), and other factors, can affect the activity and the composition of gut microbiota composition and the immunity. This is schematically presented in figure 4.

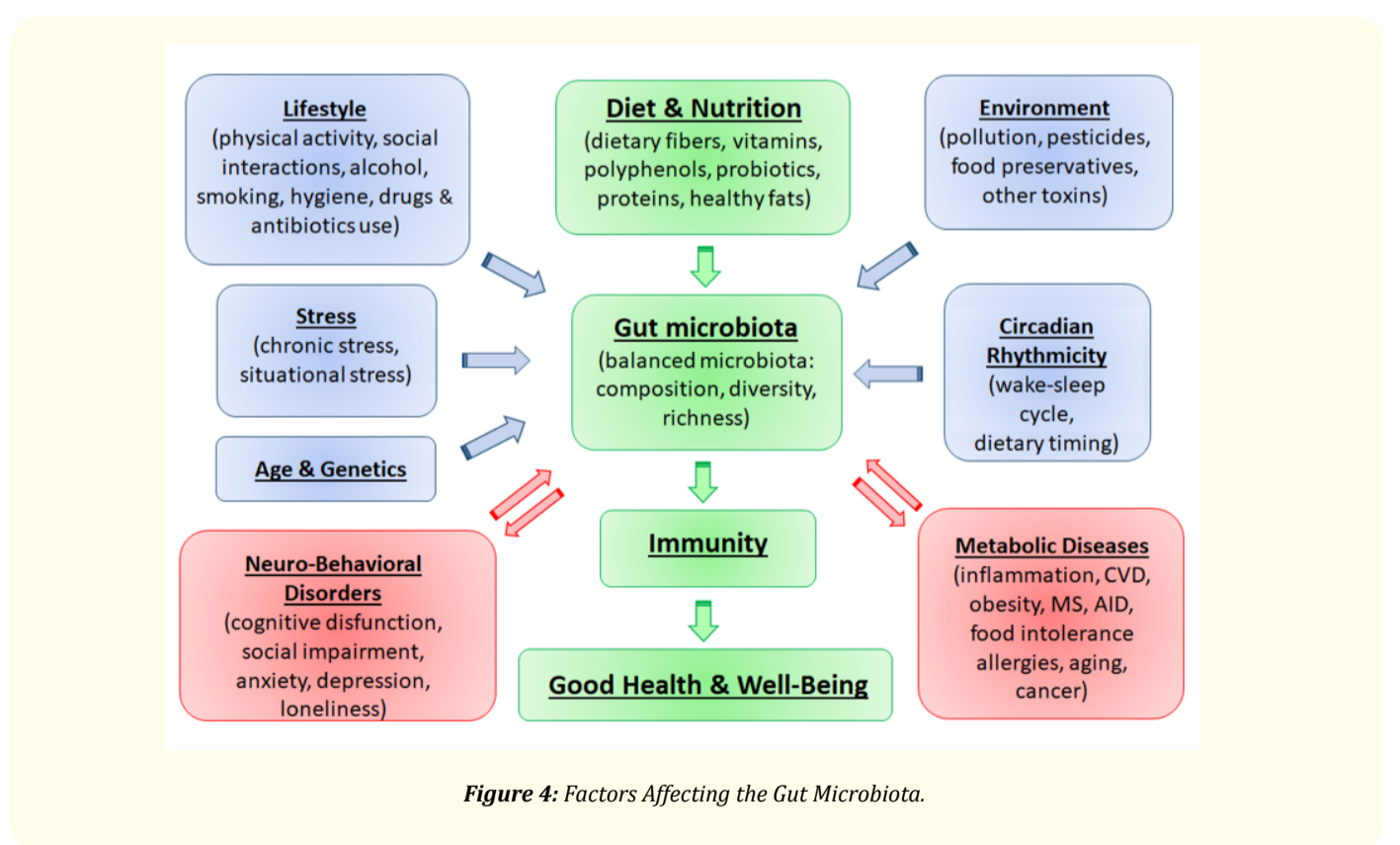


Figure 4: Factors Affecting the Gut Microbiota.

Anxiety and stress weaken the immune system. Stress is defined as homeostasis disruption due to physical, psychological or environmental stimuli (stressors), leading to adaptive behavioral and/or physiological response in order to restore homeostasis. The effect of both, the psychological and the physical stress on gut microbiome is widely recognized and has been associated with changes of the gut bacteria, which affects the brain-gut communication. Long-term stress can trigger low-grade inflammation, and consequently, reduce the immunity [235-237].

Optimism, defined as the generalized expectation that good rather than bad things will occur in life, has been related to better psychological and physical well-being. Studies have confirmed that positive thoughts and optimism may promote health, by counteracting stress-induced inflammation and might be protective for both, the physical and the mental health, especially in times of increased stress and fear. For example, the stress hormone *cortisol* has been shown to be much lower among the individuals with higher positivity [238].

Inadequate sleep suppresses the immune function. The cytokines, i.e. the proteins that the body releases during the sleep, are part of the immune system. Not enough sleep means that the body cannot make these infection-fighting proteins, which help the defense against infections. Without sufficient sleep, there is an increased risk for developing serious health problems, like heart diseases, AD, obesity and others.

Circadian rhythms are 24-hour patterns regulating the behavior and the biological functions of the organs and cells in living organisms. The gut bacteria have their own circadian rhythmicity in terms of their composition, their ability to colonize the gut, and their functions. Microbiota rhythms are regulated by the diet and the time of feeding, which means that there is rhythmicity in altering both, the microbial community structure and the metabolic activity, which impacts the host immune functions. In fact, the immune and inflammatory responses show distinct time of day dependence and appear to be regulated by the circadian mechanisms. For instance, circadian rhythm disorders damage the gut microbiota equilibrium, which damage has been associated with the occurrence of MS disorders. A study has found intestinal barrier dysfunction and disrupted gastrointestinal microbiomes in mice with disturbed circadian clocks which consequently yielded fatty liver disease and other disorders [239,240]. On the other hand, the gut bacteria modulate the host's rhythms via the microbial metabolites. Therefore, the circadian rhythms, the immune system, and the gut microbiota influence each other. Overall, disruption of the circadian rhythms can be detrimental for the organs, including the gut, and thus affects the overall physical and mental health [239-245].

Altogether, the stress, the sleep and the circadian rhythms disturbances are inter-related. This is extremely important in stressful time, like the current pandemic, when all of them are entering in a vicious cycle affecting the gut, the immunity and the mental health. For example, a circadian misalignment and/or a sleep loss could cause dysbiosis, and consequently, the resulting microbiota may contribute to the occurrence of metabolic imbalances. The reduction of sleep time or the disruption of host circadian rhythms will also lead to a physiological stress response, which will also change the host's normal intestinal microbiota. Furthermore, all these gut changes will cause host inflammatory reactions, metabolic disorders, impaired immune functions and nervous system dysfunctions. The vicious cycle continues - the host then might experience sleep problems or psychiatric symptoms. The stress can be also a reason for insomnia and depression. People with sleep disorders or depression often have anxiety symptoms, as well. The altered gut microbiota will affect the function of the brain, the nervous system and the immune system, and thus, affects the host's ability to cope with physical or psychological stress, making the host even more vulnerable to the stressful events [242].

Numerous studies have pointed out that sedentary behavior promotes a pro-inflammatory status. Also, it has been shown that *physical activity* (exercise) has a profound effect on both the adaptive and innate immune system by producing more immune cells. Exercising boosts the blood flow and enables the move of the immune cells throughout the body. Therefore, physical activity is crucial all the time, but especially in times of confinement like in the pandemic situations. It is a cost-effective method to keep the gut healthy and be resistant to infections [246-251].

Environmental pollutants especially the endocrine disrupting chemicals, such as heavy metals, particulate matter (PM), nanoparticles and others greatly influence the gut microbiome. Extended exposure to environmental pollution has been linked to food allergy and other disorders. Several animal studies have shown that alteration in the immune function, enhanced pro-inflammatory cytokine secretion, increased gut leakiness and other gut disorders occur upon exposure of the test subjects to PM, heavy metals (Pb, Cd, As) and other pollutants. What is uncertain is the ability of the gut microbiome to recover after removal of the chemical insult [252-255].

Antibiotics and other drugs' exposure can cause major shifts in microbial communities leading to mucus layer thinning, predisposing, and exacerbating infections. Antibiotic- and drug- induced microbiota imbalances, in general, alter the immune functions that normally contribute to intestinal homeostasis and infection resistance [256-258].

3.4. Mediterranean Way of Living and Gut Microbiota

Consumption of *ultra-processed food*, such as processed red meat products, products with refined sugars (cakes, cookies, refined sweetened cereals), pre-packed and ready-to eat meals, energy drinks, carbonated beverages with artificial sweeteners, high-fat milk products, and others can lead to severe dysbiosis. High intake of processed food containing animal-derived proteins, saturated and trans fats, refined sugars and salt, and poor in nutrients, such as natural antioxidants, omega-3 fatty acids, and fiber content, could stimulate the growth of pathogenic bacteria on the account of beneficial bacteria, leading to potential alterations of the gut and the intestinal barrier. For instance, Western diets [259-261] comprising mainly processed food have been shown to enhance *Escherichia coli* colonization and associated inflammation in mice by altering the host mucus layer, increasing intestinal permeability, and impairing the immune function. Moreover, such dietary patterns may cause the activation of the innate immune system, most likely by excessive production of proinflammatory cytokines and reduced production of anti-inflammatory cytokines. The impaired gut epithelial barrier and disturbances in the intestinal microbiota will eventually result in a chronic mucosal inflammation, and subsequent increases in chronic non-communicable diseases, such as obesity, CVDs, AIDs, type 2 diabetes, and colon cancer [190,259-266].

On the other hand, the protective effects of the Mediterranean diet against chronic diseases are attributed to the cumulative synergistic and interactive combination of its nutrients. In the context of gut health, MD promotes diverse and rich microbiota and these positive changes have been attributed to MD as a consistent source of key nutrients, including dietary fibers, omega-3 fatty acids and crucial vitamins, such as vitamins C, B6, B9, B12, and D, and minerals such as zinc, copper, selenium, potassium, iron, manganese, and magnesium. The consumption of dietary fibers and plant proteins has also been associated with an increase of beneficial bacteria quantity stimulating SCFA production and other associated metabolites. Comparison of consumption level of certain foods in the Mediterranean and Western diets is given in table 1.

Food	Mediterranean	Western
Fruits and vegetables (fresh, minimum-processed)	High	Low
Whole grains (unrefined cereals, oats, brown rice)	High	Low
Legumes (beans, lentils, chickpeas)	High	Low
Nuts (walnuts, hazelnuts, pistachio, peanuts)	High	Low / Moderate
Fish, seafood (salmon, tuna, shellfish)	Moderate	N/A
Poultry (chicken, turkey)	Moderate	Moderate / High
Processed red meats (sausages, hamburgers)	Low	High
Refined sugars (sweets, sweetened beverages)	Low	High
Extra-virgin olive oil	High	Low
Red wine	Moderate	N/A

Table 1: Comparison of Consumption Level of Certain Foods in Mediterranean and Western diets.

Two recent randomized controlled trials are linking MD to the positive changes in the gut - a more stable gut ecosystem characterized with richer populations of the bacteria that produce beneficial metabolites (SCFAs) and reduced levels of pathogenic bacteria. This is consistent with a study, which reported that high adherence to MD is related to decreased counts of *E. coli*, a representative of the pathogenic bacterium, as well as increased ratio of a typical beneficial *Bifidobacteria:E. coli*, which is considered an important indicator for gut microbiota equilibrium and overall health [132,133].

Another study showed that a high-fiber-rich MD tested against an animal fat-rich low-fiber diet can alter the human gut microbiome composition in just four days. The dietary pattern low in fiber and high in sugar and saturated fat shifts the microbiome toward a profile that has been associated with chronic metabolic diseases, whereas the MD rich in fiber, unsaturated healthy fats (MUFA), polyphenols and other phytonutrients shifts the microbiome and plasma microbial metabolites towards a gut microbial profile that has been associated with beneficial health effects [181].

Due to the high consumption of plant-based foods, significantly higher levels of total SCFAs as metabolic products of the dietary fibers have been detected in people with high-level adherence to MD than in people on Western diets. Furthermore, bioactive substances such as polyphenols - plant compounds abundant in the Mediterranean dietary pattern, have been associated with improved microbial diversity that correlates with improved mood, cognition and cardiovascular health, as well as enhanced blood flow to the brain. Omega-3 fatty acids and micronutrients in MD appear to have the potential to reduce the systemic inflammation, reduce the intestinal permeability, and further promote the gut microbiota diversity and stability. Toribio-Mateas^[172] even coined the phrase "*Mediterranean gut*" for a healthy and resilient gut with diverse microbiota like those found in people adhering to the MD [174-181,265-269].

Several studies have proved Mediterranean Diet as an *anti-inflammatory diet* showing evidence that it reduces systemic inflammation by promoting a healthy microbiota. When compared to diets comprising mostly animal-based products, MD has shown to significantly reduce inflammatory biomarkers. MD as an anti-inflammatory diet is being also recommended to patients to enhance the effects of pharmacological therapies in treatment of several inflammatory diseases. For instance, MD has been shown to improve the quality of life and well-being of patients already having health issues, such as RA and irritable bowel disorder. MD can be neuroprotective, as well. Several dietary components consumed in the MD (omega-3 fatty acids, antioxidants) can inhibit neuro-inflammation processes associated with disorders, like AD [270-280].

Chronic, systemic inflammation is believed to be one of the leading drivers of some of the most serious conditions, such as obesity, type 2 diabetes, MS, CVDs, AD, depression, and others. *Obesity* for instance is a low-grade chronic inflammatory state that has been linked to an increased risk for viral and bacterial infections. In fact, the obesity can modify innate and adaptive immune responses, making the immune system more vulnerable to infections and less responsive to vaccinations, as well as can contribute to the onset of metabolic diseases. Therefore, maintaining a *healthy weight* can significantly benefit the immune system. A plant-based diet, like MD, is an effective diet for maintaining a healthy weight due to its abundance of dietary fibers, which helps the *feeling of satiety*, without adding extra "bad" calories [269,281].

Adequate sleep and undisturbed circadian rhythms are very important for maintaining strong immune system. Several studies have shown positive effects of MD on sleep patterns in different population groups [282-284]. Consuming foods containing tryptophan (roots, bananas, cherries, whole grain oats) during dinner time, could improve the sleep quality. Tryptophan is an essential amino acid, which is actually involved in the metabolic production of serotonin and melatonin, important for the sleep quality. In fact, 95% of serotonin is produced and stored within the cells of the gut [282].

Obviously, the interplay among the microbiota, genetics, age, diet, stress, physical activity, and environment is a complex process influencing both, the mental and the physical health. By adopting a healthy diet and lifestyle, such as the Mediterranean way of living, healthy and diverse microbiota, strong immune system and suppressed inflammatory processes are possible. It seems that the "*Mediterranean gut*" might be a solution to many metabolic diseases and mental disorders.

4. Summary

The discovery of high percentage of longer-living people with good cognitive functions and low incidence of cardiovascular, cancer and metabolic diseases in the Mediterranean countries in 60's, which was attributed to their diet and lifestyle, led to numerous studies on the MD making it one of the most studied diets in the world. MD emphasizes consumption of fruits, vegetables, whole grains, legumes, nuts, seeds, and EVOO, while the consumption of animal-derived foods, such as processed red meat and products with refined sugars is limited. Moderate consumption of fish, seafood, poultry and fermented dairy and non-dairy products with a red wine consumed with the meal are also characteristics of MD. The efficacy of this diet has been attributed to its variety of nutrients and their anti-oxidative and anti-inflammation effects, which result in maintenance of a healthy gut and strong immune responses, and the overall good health in the Mediterranean populations.

To-date, Mediterranean way of living has been recognized as one of the healthiest dietary and lifestyle patterns in the world due to its nutrient-packed dietary choices and distinct lifestyle aspects emphasizing conviviality, social interactions, adequate sleep, rest and leisure activities, and most importantly, enjoying the life. Having positive mindset is what we need the most in the time of worldwide pandemic. While social interactions are restricted at the moment, there are many ways that we can still stay socially-connected, communicate with each other, take care, encourage and help each other, and thus, experience the feeling of community - an important aspect of the Mediterranean way of living.

Mediterranean way of living is an affordable, easy-to-follow diet and lifestyle habits for maintaining a healthy and resilient "*Mediterranean gut*", which could protect us from infections and metabolic diseases. Moreover, MD has been called an "*evergreen solution*" for optimal modulation of microbiota diversity and stability and even has been mentioned as a "*food pharmacy*" for immunological modulation through a diet [174,175].

As we started, we will finish with another Hippocrates quote: "*Let food be thy medicine and medicine be thy food*". This time, Hippocrates is absolutely right - his quote remains highly relevant after millennia. Surprisingly, the diet of his origin country - the Mediterranean diet - could be the *medicine* that we all need today. With the Mediterranean healthy lifestyle and adequate nutrition, we could all emerge strong from the current pandemic situation and will be able to quickly adapt to "the new normal" life situations.

Acknowledgement

The authors sincerely acknowledge the support of CSI: Create. Solve. Innovate. LLC and its MD Inspired™ concept for promoting the Mediterranean way of living outside the Mediterranean region.

Conflict of Interest

Authors declare no conflict of interest.

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Volume 16 Issue 1 January 2021

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