

REVIEW

Modern vision of the Mediterranean diet

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Summary

The Mediterranean diet is the most well-known and researched dietary pattern worldwide. It is characterized by the consumption of a wide variety of foods, such as extra-virgin olive oil (EVOO), legumes, cereals, nuts, fruits, vegetables, dairy products, fish, and wine. Many of these foods provide several phytonutrients, among which polyphenols and vitamins play an important role. Data from several studies have strongly established that nutrition is a key factor in promoting a healthy lifestyle and preventing many chronic diseases. In particular, a large number of studies have established the protective effects of the Mediterranean diet against several chronic diseases, among which are diabetes, cardiovascular diseases, cancer, aging disorders, and against overall mortality. Animal and human translational studies have

revealed the biological mechanisms regulating the beneficial effects of the traditional Mediterranean diet. Indeed, several studies demonstrated that this nutritional pattern has lipid-lowering, anticancer, antimicrobial, and anti-oxidative effects. Moreover, the Mediterranean diet is considered environmentally sustainable. In this review, we describe the composition of the Mediterranean diet, assess its beneficial effects, and analyze their epigenomic, genomic, metagenomic, and transcriptomic aspects. In the future it will be important to continue exploring the molecular mechanisms through which the Mediterranean diet exerts its protective effects and to standardize its components and serving sizes to understand more precisely its effects on human health.

Introduction

The Mediterranean diet (MD), defined by Ancel Keys in the 1960s, is one of the most well-known and well-researched dietary patterns worldwide [1]. The MD is the traditional dietary pattern followed by the inhabitants of the Mediterranean region. Historically, in the countries close to the Mediterranean Sea, the main diet has included an abundance of different non-starchy vegetables, seeds, nuts, marginally refined whole-grain cereals, and legumes [2]. Since the 1960s, MD has been extensively studied to understand its role in the prevention of chronic and/or degenerative diseases, cardiovascular diseases, metabolic syndrome, cognitive decline, and cancer [3]. Furthermore, MD is considered an environmentally sustainable dietary pattern [4]. Specifically, an epidemiological study revealed the association of MD with the decreased incidence of cardiovascular diseases [5]. Similarly, other observational and epidemiological studies reported an inverse relationship of MD with disease risk and mortality in various types of cancers [6-8]. The interventional trial PREDIMED (Prevención con Dieta Mediterránea) compared MD with the control diet and documented a significant reduction in the incidence of diabetes and cardiovascular diseases in the MD group [8].

A recent meta-analysis based on observational studies and clinical trials highlighted the beneficial effects of MD on various chronic diseases, such as cardiovascular diseases, diabetes, myocardial infarction, coronary heart disease, neurodegenerative diseases, cancer incidence, and overall mortality [9, 10]. Furthermore, studies have analyzed the effects of MD on cognitive function, aging parameters, and improvement in quality of life [11]. MD has been linked to the healthy aging concept, which is defined as the lack of major chronic diseases, good mental and physical condition, absence of depression, absence of function-limiting pain, good social functioning, and independent performance of daily activities [8].

Mediterranean diet components and their characteristics

A significant feature of MD is the daily consumption of several phytonutrients, such as plant phenols and vitamins as follows.

EXTRA-VIRGIN OLIVE OIL (EVOO)

One of the main characteristics of MD is the regular consumption of EVOO, which contains a mixture of essen-

tial dietary fatty acids. The consumption of olive oil is considered the main reason for a long life span amongst Mediterranean populations [1]. EVOO is the major source of unsaturated fatty acids and other components, such as fat-soluble vitamins, polyphenols, chlorophylls, and phytosterols [12, 13]. The polyphenols present in olive oil possess anti-inflammatory, antioxidant, neuro-protective, cardioprotective, anticancer, anti-obesity, anti-diabetic, antimicrobial, and antisteatotic effects. These effects are mainly caused by the presence of secoiridoid (anti-feeding deterrents of the *Oleaceae* family, such as iridoid glycoside) derivatives, among which oleuropein, oleacein, and oleocanthal, and simple phenols, such as tyrosol and hydroxytyrosol [3, 14-20].

LEGUMES, CEREALS, AND NUTS

Humans have been cultivating legumes for centuries and consuming them in the form of porridge and pulses. Pulses are highly nutritious and can be easily prepared and stored for long periods. Undoubtedly, these features of legumes are the cause for their success and their incorporation in the traditional diets of various countries. The most common legumes of MD are beans, lentils, and chickpeas. Legumes are usually mixed with different cereals, fish, meat, and vegetables. Similarly, for thousands of years, seeds and nuts (hazelnuts, almonds, tree nuts, pistachios, etc.) have been considered a staple food and consumed daily. Nuts and legumes have been routinely consumed all over the Mediterranean region, Asia, and America [1]. The main components of pulses and beans are flavanols, a type of polyphenols with a ketone group in their chemical formula, which reduce endothelial dysfunction, decrease cholesterol and blood pressure, and regulate energy metabolism [21]. Moreover, people living in the Mediterranean countries regularly consume cereals, such as rice and wheat, in the form of pasta, bread, couscous, etc. These cereals, along with potatoes, constitute the main sources of energy and carbohydrates [1].

FRUITS AND VEGETABLES

The Mediterranean climate favors the production of several vegetables and fruits that constitute a major part of MD. Original Mediterranean vegetables include turnips, artichokes, lettuce, and radishes. Interactions with outside regions led to the introduction of new varieties of fruits and vegetables. For example, citrus fruits and eggplant were introduced from North Asia and India, whereas zucchini, tomatoes, potatoes, peppers, corn, and green beans entered the Mediterranean region from the Americas [1].

DAIRY PRODUCTS

Traditionally, the consumption of milk and other dairy products has been low in the Mediterranean countries. However, plenty of land is devoted for raising goats and sheep for their meat, milk, and wool, thus facilitating the manufacture of yogurt, cheese, and other fermented dairy products [1].

FISH

The Mediterranean region possesses a rich tradition of fishing, which has led to high fish consumption. However, environmental contaminants have compromised the contributions of omega-3 fatty acids [1].

WINE

In the European Mediterranean countries, MD has been significantly associated with moderate wine consumption during meals. Wine is known to have originated during the Neolithic period, while the Greeks and Egyptians popularized the beverage by developing the techniques related to its refinement and preservation. Moreover, Romans extended grapevine cultivation across Italy and other countries, hence making wine an essential part of MD [1].

Mechanisms involved in Mediterranean diet effects

Latest advancements in all omics fields and bioinformatics have allowed their use in nutritional studies for enhancing the understanding of molecular mechanisms and changing paradigms [8, 22].

Mediterranean diet and transcriptomics

The use of transcriptomics makes it possible to analyze the specific effect of a diet or food on gene expression, thereby leading to a better understanding of specific mechanisms. It is possible to unravel which gene expression is upregulated or downregulated by the influence of certain foods. In humans, several researchers have analyzed the effects of MD and its components on the transcriptome using selected candidate genes as well as the whole transcriptome. The PREDIMED study has examined alterations in canonical pathways of the cardiovascular system. Nine of these pathways were altered by MD + virgin olive oil, whereas four pathways were modified by MD + nuts. Overall, the results showed that MD modulates crucial pathways associated with cardiovascular risk, such as renin-angiotensin, atherosclerosis, hypoxia, angiopoietin and nitric oxide signaling, and endothelial nitric oxide synthase signaling pathways. This finding supports the idea that MD could exert beneficial effects by altering the expression of genes associated with cardiovascular diseases. Interestingly, the study noted that the atherosclerosis signaling pathway was significantly downregulated after the MD + EVOO intervention (Tab. I) [23, 24].

Mediterranean diet and epigenomics

The term epigenomics refers to a wide range of genomic modifications without involving changes in the DNA sequence, which lead to alterations in gene expression. The epigenomic profile may be linked to increased car-

Tab. I. Genes of the atherosclerosis signaling pathway that were downregulated after the MD + EVOO intervention.

Gene symbol	Gene name
IL1RN	Interleukin 1 receptor antagonist
IL1 β	Interleukin 1-beta
ICAM1	Intercellular adhesion molecule 1
TNF- α	Tumor necrosis factor, alpha

Tab. II. Immune and inflammatory-linked genes for which methylation pattern was modified by 5 years of MD in peripheral blood cells.

Gene symbol	Gene name
EEF2	Eukaryotic translation elongation factor 2
IL4I1	Interleukin 4-induced gene 1
COL18A1	Collagen, type xviii, alpha-1
PLAGL1	Plag1-like zinc finger 1
LEPR	Leptin receptor
PPARGC1B	Peroxisome proliferator-activated receptor-gamma, coactivator 1, beta
IFRD1	Interferon-related developmental regulator 1
MAPKAPK2	Mitogen-activated protein kinase-activated protein kinase 2

diovascular risk and aging [25]. Three types of epigenetic biomarkers are often observed based on epigenetic regulators: DNA methylation, noncoding RNA synthesis, and histone modification. A study involving 36 participants investigated the alterations induced in the methylome of peripheral blood cells after 5 years of MD (Tab. II) [26]. Similar results were obtained by studies that evaluated the effects of MD on inflammation at the epigenetic level [8, 27, 28].

Mediterranean diet and genomics

The first omics approach was focused on the study of single nucleotide polymorphisms that influence diseases associated with the metabolic status. With technological advancements, genome-wide association studies and, subsequently, next-generation sequencing technologies were applied to explore multiple polymorphisms in a single experiment [29-31]. Currently, studies focusing on gene-diet interactions are involved in examining the heterogenic responses of identical dietary patterns, which means that different individuals exhibit different responses to the same MD components. PREDIMED revealed that polymorphisms in specific genes associated with cardiovascular disease risk display significant gene-diet interactions with MD (Tab. III) [8]. The influence of MD on microRNA-binding site polymorphisms was observed via the analysis of the gain-of-function mutation polymorphism (rs13702) of microRNA-410 in the *LPL* 3'-untranslated region. The findings revealed a gene-diet interaction and demonstrated that MD enhanced reduced triglyceride concentrations and stroke risk, whereas in the control diet, these beneficial effects were lost [8, 32].

Mediterranean diet and metagenomics

The gut microbiota plays an important role in the relationship between dietary habits and health. Several studies analyzed the effect of MD components on microbiota, both at the species level and at the metagenomic level. Some of the studies reported beneficial effects of MD on the microbiota, and other studies examined the favorable effects of MD on health by simulating the profiles of beneficial microbiota. Moreover, the presence of metabolomic markers in urine or plasma indirectly reflect the microbiota activity. The incorporation of metabolomics and metagenomics, along with exposomics (the study of all the exposures of an individual in a lifetime and how those exposure relate to health) and genomics, will certainly provide informative results on the mechanisms of action of MD in the years to come [8, 33, 34].

Mediterranean diet and bioinformatics

Computational and bioinformatic methods play a vital role in investigating the effects of MD. The latest bioinformatic tools and highly efficient data-generation methods have enabled the collection of huge amounts of information and rapid analyses of data. Currently, various bioinformatic tools and techniques, such as networking and pathway analyses, are being applied to understand the complexity of MD effects at the systems biology level. Significant advancements are expected in the near future, which are likely to enable us to better understand the molecular basis of the multidimensional effects of MD [8, 35, 36].

Effects of the Mediterranean diet on disease pathways

MD exerts many beneficial effects on human health and prevents chronic diseases via various mechanisms.

LIPID-LOWERING EFFECTS

The initial mechanistic studies explaining the inverse relationship of MD with cardiovascular risk focused on high monounsaturated fatty acid and low saturated fatty acid contents of MD. These studies also examined other conventional risk factors, such as plasma lipid concentration, glucose metabolism, and blood pressure [8, 37, 38]. The results of the PREDIMED study showed that MD is able to improve the protective role of

Tab. III. Genes for which polymorphisms are associated with cardiovascular disease risk and display significant gene-diet interaction with MD.

Gene symbol	Gene name
MLXIPL	Mlx-interacting protein-like
TCF7L2	Transcription factor 7-like 2
CLOCK	Circadian locomotor output cycles kaput
LPL	Lipoprotein lipase

HDL by reversing cholesterol transport and enhancing cholesterol efflux capacity via reduction of the activity of cholesteryl ester transfer protein, thereby increasing HDL's ability of cholesterol esterification and its vasodilation capacity [39, 40].

PROTECTION AGAINST OXIDATIVE STRESS AND INFLAMMATION

Traditional MD is rich in antioxidant components such as vitamin E, β-carotene, vitamin C, and flavonoids, minerals such as selenium, and natural folate [2]. The results of a large case-control study called INTERHEART revealed the beneficial effect of dietary antioxidants on coronary heart disease [41]. Insufficient intake of dietary antioxidants might escalate the risk of atherosclerotic plaque formation owing to alterations in lipoprotein oxidation. Recently, the participants of a randomized clinical trial who adhered to an MD + EVOO dietary pattern demonstrated a significant decrease in inflammatory markers and oxidized circulating LDL [42]. The PREDIMED study showed that MD exerts anti-inflammatory effects on the cardiovascular system and is able to reduce both systolic and diastolic blood pressure [43]. Specifically, PREDIMED reported that serum levels of several genes decreased after 3-5 years of MD intervention (Tab. IV) [44].

Oxidative, inflammatory, and nitrosative stresses are the most common causes for neurodegeneration, whereas antioxidant molecules, such as polyphenols from olive oil, restore neuronal function by improving the redox status. Additional beneficial effects of MD include hypoglycemic, antioxidant, antiviral, antimicrobial, cardioprotective, antitumor, anti-inflammatory, neuroprotective, and antiaging effects [45].

In transgenic mouse models of Alzheimer's disease, hydroxytyrosol was found to alleviate oxidative stress in the brain and mitochondria as well as neuroinflammation by inducing the expression of the Nrf2-dependent gene. Similarly, the administration of oleuropein for 8 weeks at a dose of 60 mg/kg/day was able to decrease oxidative stress and increase mitochondrial function via activation of the Nrf2 pathway in spontaneously hypertensive rats. Moreover, tyrosol, at a dose of 240 mg/kg, was able to offer protection against lipopolysaccharide-induced acute lung injury via inhibition of NF-κB and activation of AP-1 and Nrf-2 pathways [3, 46].

Tab. IV. Genes for which serum levels decreased after 3–5 years of MD intervention.

Gene	Gene name
IL-6	Interleukin 6
IL-8	Interleukin 8
IFN- γ	Interferon, alpha-1
IL-5	Interleukin 5
IL-7	Interleukin 7
IL-1β	Interleukin 1-beta
TNF-α	Tumor necrosis factor, alpha
IL-12p70	Interleukin 12

In an animal model of rheumatoid arthritis, the phenolic extracts of EVOO protected the joints and decreased proinflammatory mediators via inhibition of MAPK and NF-κB signaling in activated synovial fibroblasts. In the same model, the polyphenolic extracts of EVOO inhibited IL-6, TNF-α, IL-1β-induced matrix metalloproteinases, microsomal PGE synthase-1, and IL-1β-induced cyclo-oxygenase-2 [3, 47].

ANTICANCER EFFECTS

Since the last decade, several *in vivo* and *in vitro* studies have revealed anticancer effects of hydroxytyrosol from olive oil against numerous malignant cell types, which could be attributed to different mechanisms of action. Most of the studies have been focused on colon cancer, which is the third most prevalent cancer worldwide and is associated with a high death rate in developing countries. Because of its autooxidation properties, the accumulation of H₂O₂ is considered one of the most significant anticancer mechanisms of hydroxytyrosol. However, several studies have highlighted the proapoptotic and antiproliferative mechanisms of hydroxytyrosol based on the type of cancer cells studied [48, 49]. The analysis of androgen-dependent prostate cancer cells showed that hydroxytyrosol inhibits the expression of the androgen receptor and androgen receptor-responsive prostate-specific antigen secretion [50].

Furthermore, in hepatocellular carcinoma cells, hydroxytyrosol exerts anticancer effects by inhibiting proliferation and inducing apoptosis and G2/M cell cycle arrest. Moreover, hydroxytyrosol could lead to angiogenesis and tumor growth inhibition *in vivo* via the inhibition of NF-κB and PKB/Akt pathways. The proapoptotic and antiproliferative effects of hydroxytyrosol are also linked to inhibition of the lipogenic enzymes farnesyl diphosphate synthase and fatty acid synthase in human hepatoma cells, which are related to aggressive tumor behavior [51].

ANTIDIABETIC EFFECTS

Several *in vivo* animal studies on diabetes have established the beneficial effect of oleuropein or olive leaf extracts rich in oleuropein against type 2 diabetes. Clinical trials that enrolled people with type 2 diabetes mellitus have reported significant reductions in fasting plasma glucose levels and glycated hemoglobin levels after treatment with 500 mg/day of olive leaf extracts for 14 weeks. Another clinical trial on overweight middle-aged men reported significant improvement in the responsiveness of pancreatic β-cells and insulin sensitivity after supplementation with olive leaf extracts, 51 mg oleuropein, and 9.7 mg hydroxytyrosol on a daily basis [14, 52].

In animal model of diabetes, significant reductions in serum glucose, oxidative stress, and cholesterol levels were observed after oleuropein treatment. Moreover, oleuropein promoted glucose-stimulated secretion of insulin in pancreatic β-cells via the stimulation of the ERK/MAPK signaling pathway and inhibition of amylin

amyloid cytotoxicity, which is the most prominent characteristic of type 2 diabetes [53, 54].

ANTIATHEROGENIC EFFECTS

Oleuropein and hydroxytyrosol present in MD inhibit monocyte cell adhesion and endothelial activation. These effects are attributed to the antioxidant and anti-inflammatory activities of oleuropein and hydroxytyrosol [14, 55, 56].

EFFECTS ON AUTOPHAGY

Autophagy is essential for the efficient development and functioning of cardiomyocytes. Moreover, the process plays a vital role in regulating the inflammatory response produced by macrophages, most likely via restriction of the activity of inflammasomes and generation of macrophage foam cells by lipid turnover modulation. Autophagy also modulates neurodegenerative diseases and metabolism dysregulation. Therefore, the beneficial effects of MD might influence the regulation of autophagy [57, 58].

Researchers have observed that polyphenols from MD exert a direct effect on autophagy. Resveratrol, a polyphenol present in nuts, wine, and grapes, is an autophagy inducer [59]. The effects of resveratrol on autophagy might be explained by its enhancing effect on the activity of deacetylase sirtuin 1, which in turn regulates the activity of several autophagy-related proteins. Likewise, polyphenols present in virgin olive oil, such as oleocanthal and oleuropein, have been reported to enhance autophagy [8, 60].

MODIFICATION OF HORMONES AND GROWTH FACTORS

Short-chain fatty acids that are produced by the metabolism of oligosaccharides and resistant starch present in MD by the gut microbiota can induce satiety by obstructing gastric emptying, thereby increasing the production of gut hormones, such as glucagon-like peptide-1 and peptide-YY. Importantly, in addition to weight loss, MD causes a substantial decrease in fasting glucose and C-peptide levels as well as free and total testosterone levels [61].

In women, MD causes a significant increase in plasma levels of sex hormone binding globulin and insulin-like growth factor binding protein 1 and 2, which reduce the biological activity of estradiol, insulin-like growth factor 1, and testosterone [62]. Additionally, lower glycemic index, lower branched-chain amino acid intake, and higher monounsaturated and n-3 fatty acid intake might exert beneficial effects in decreasing insulin resistance along with compensatory hyperinsulinemia [63, 64]. Furthermore, the high fiber contents of MD could increase fecal mass and estrogen excretion, which results in decreased plasma levels of estradiol and estrone [65]. The vegetables present in MD are rich in chemical compounds that offer potential benefits against different types of cancer, such as lycopene in tomato; organosulfur compounds in onion and garlic; capsaicin in hot pepper; indol-3-carbinol, isothiocyanates, and sulforaphane

in cruciferous vegetables; monoterpenes in oranges and lemons; polyacetylenes in pumpkin and carrots; spermidine and ferulic acid in whole grains; and ginkgetin in capers. Moreover, estrogenic molecules with low potency, such as biochanin A, formononetin, daidzein, coumestans, and genistein found in beans, can compete with the endogenous estrogens for binding to estrogen receptors, hence blocking their mitogenic effects [2, 66].

ANTIMICROBIAL AND ANTIVIRAL EFFECTS

Studies have reported that hydroxytyrosol exhibits *in vitro* antimicrobial properties against various gastrointestinal tract and respiratory infectious agents, such as *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Haemophilus influenzae*, *Salmonella typhi*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, at reduced inhibitory concentrations as well as foodborne pathogens, such as *Listeria monocytogenes*, *Yersinia enterocolitica*, and *Salmonella enterica*. Furthermore, the antimicrobial activities of hydroxytyrosol oleate and hydroxytyrosol acetate against *Staphylococcus epidermidis* and *Staphylococcus aureus* were evaluated [67, 68]. The results from such studies established that hydroxytyrosol inhibits the hemolytic activity of streptolysin O released by *Streptococcus pyogenes*. Additionally, hydroxytyrosol demonstrates antibacterial activity against *Propionibacterium acnes* and mycoplasmas, such as *Mycoplasma pneumoniae* [69]. Hydroxytyrosol also appears to display inhibitory properties against human immunodeficiency virus (HIV)-1, preventing it from entering the host cell and binding to its catalytic site, thus inhibiting viral entry and integration. Studies have also reported the inactivation of influenza A viruses by hydroxytyrosol, thus suggesting that the antiviral mechanism of hydroxytyrosol might require the presence of the viral envelope [14, 70]. Finally, hydroxytyrosol exerts a similar antiviral mechanism against SARS-Cov-2 virus, resulting in a potential treatment benefit against COVID-19 infection [71-75].

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; AKK, MCM, GB, BA, VV, GM, AI, LS, STC, KLH: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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