

Mediterranean diet and inflammaging within the hormesis paradigm

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A coherent set of epidemiological data shows that the Mediterranean diet has beneficial effects capable of preventing a variety of age-related diseases in which low-grade, chronic inflammation/inflammaging plays a major role, but the underpinning mechanism(s) is/are still unclear. It is suggested here that the Mediterranean diet can be conceptualized as a form of chronic hormetic stress, similar to what has been proposed regarding calorie restriction, the most thoroughly studied nutritional intervention. Data on the presence in key Mediterranean foods of a variety of compounds capable of exerting hormetic effects are summarized, and the mechanistic role of the nuclear factor erythroid 2 pathway is highlighted. Within this conceptual framework, particular attention has been devoted to the neurohormetic and neuroprotective properties of the Mediterranean diet, as well as to its ability to maintain an optimal balance between pro- and anti-inflammaging. Finally, the European Commission-funded project NU-AGE is discussed because it addresses a number of variables not commonly taken into consideration, such as age, sex, and ethnicity/genetics, that can modulate the hormetic effect of the Mediterranean diet.

INTRODUCTION

An enormous variety of stimuli (chemical, physical, biological, psychological) can be sensed as stressors by organisms, leading to physiological reactions through a nonspecific response referred to as a stress response.¹ The stress response can spread at the systemic level through the production and secretion of hormones, cytokines, and neurotransmitters aimed at the modulation of the neuroendocrine and immune systems.^{2,3} During evolution, neuroendocrine and immune functions are

managed by a unique cellular protagonist, the macrophage, within an integrated and conserved defense network.^{4,5} On the basis of this evolutionary perspective, it was conceptualized that immune and stress responses functionally overlap and that classic “antigens” (viruses and bacteria, but also food) can be considered stressors that were likely major selective forces for the evolution of the immune system.^{6,7}

A stressor can prove deleterious or beneficial depending on the reaction it evokes, which, in turn, depends on the intensity and persistence of the stressor

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itself, as well as on the individual's capacity to cope with it.¹ In this context, it is important to discriminate between acute stress, associated with a quick and short-term response, and chronic prolonged stress. At variance with acute stress, chronic stress is much more difficult to define and quantify because of its relatively lower intensity and longer persistence; its outcome can also be either a progressive adaptation or a progressive deterioration.^{1,8}

Counterintuitively, exposure to very low doses of a substance that is toxic at high doses can elicit beneficial effects. This phenomenon (mithridatism) was conceptualized in 1538 by Paracelsus, who wrote: “[A]ll things are poison and not without poison; only the dose makes a thing not a poison.” In 1887, H. Schulz demonstrated for the first time that a toxic substance may induce opposite effects depending on the dose (Arndt Schulz Law).⁹ In more recent years, the beneficial effect of exposure to low-grade potentially damaging conditions or very low doses of otherwise toxic compounds has been conceptualized as “preconditioning” and “hormesis.” The term *hormesis*, coined within the toxicology field, defines adaptive, nonmonotonic, biphasic dose-response relations following an initial disruption in homeostasis (Figure 1).¹⁰ In the framework of this conceptualization, the activation and upregulation of cellular and molecular defense pathways due to mild stressors and the subsequent adaptation and protection are named pre- and postconditioning, respectively.^{11,12} The biological importance of these concepts—particularly of hormesis—is far reaching because they may represent the most satisfactory explanation of a variety of complex phenomena. In this regard, it is important to highlight that the health effects of the most thoroughly studied topic in the aging/nutrition field (ie, calorie restriction) have been conceptualized within the hormesis paradigm.^{11,13} The main mechanisms involved are stress-activated cellular pathways, such as heat shock protein (HSP) response, unfolded protein response, DNA damage response, sirtuin response, autophagy, antioxidant system activation, and inflammation.^{14,15}

INFLAMMAGING AND THE MEDITERRANEAN DIET

It is widely accepted that old age is characterized by a peculiar low-grade, chronic, and “sterile” inflammatory state, which has been termed *inflammaging*.^{7,16,17} Inflammation has likely been selected during evolution for its beneficial role in fighting infections and facilitating tissue repair in the early phases of life. However, it appears that, with aging, the load of exogenous and endogenous stressors capable of eliciting inflammatory responses gradually increases unabated, leading to high

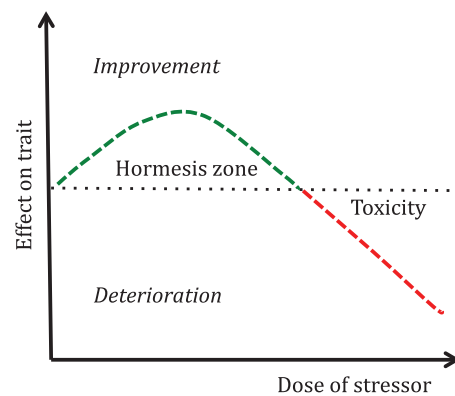


Figure 1 Biphasic dose-response curve toward a hormetic stimulus. Under a certain threshold, the effect of a stimulus/stress on the measured trait is positive (improvement), whereas over this threshold it becomes detrimental/toxic. The range of hormetic doses is indicated as the “hormesis zone.”

levels of proinflammatory mediators, which are believed to substantially contribute to the pathogenesis of many, if not all, age-associated diseases and to the progression of the aging process.^{16,17} Inflammaging likely results from the imbalance between the production of pro- and anti-inflammatory mediators in a sort of adaptive mechanism to a person's lifelong exposure to stressors, whereby inflammation continuously triggers anti-inflammatory responses.¹⁸ In this context, good nutrition, particularly as provided by the Mediterranean diet (MedDiet), could represent a powerful tool to profoundly remodulate this systemic inflammatory balance on a long-term scale by slowing down the age-related increase in the production of inflammatory molecules and by favoring adaptive anti-inflammatory responses. The MedDiet may, therefore, shift the age at which this ratio (pro-/anti-inflammation) trespasses beyond the threshold that separates physiological inflammation from unbalanced pro-inflammation, which, in turn, favors age-related inflammatory diseases (Figure 2). It can be surmised that the effect of the MedDiet on inflammaging, in a fashion similar to the one proposed to explain the effects of calorie restriction, is hormetic. In other words, specific components of the MedDiet likely minimize the increase of inflammatory stimuli by acting as hormetins.

Inflammaging could, in turn, be considered a sort of hormetic stress, having positive outcomes at low doses (physiological inflammation) at young and adult ages and becoming detrimental during the post-reproductive period, especially in people who, as a result of genetic background and/or unhealthy lifestyle, including poor nutrition, are not able to maintain an optimal balance between inflammaging and anti-inflammaging.

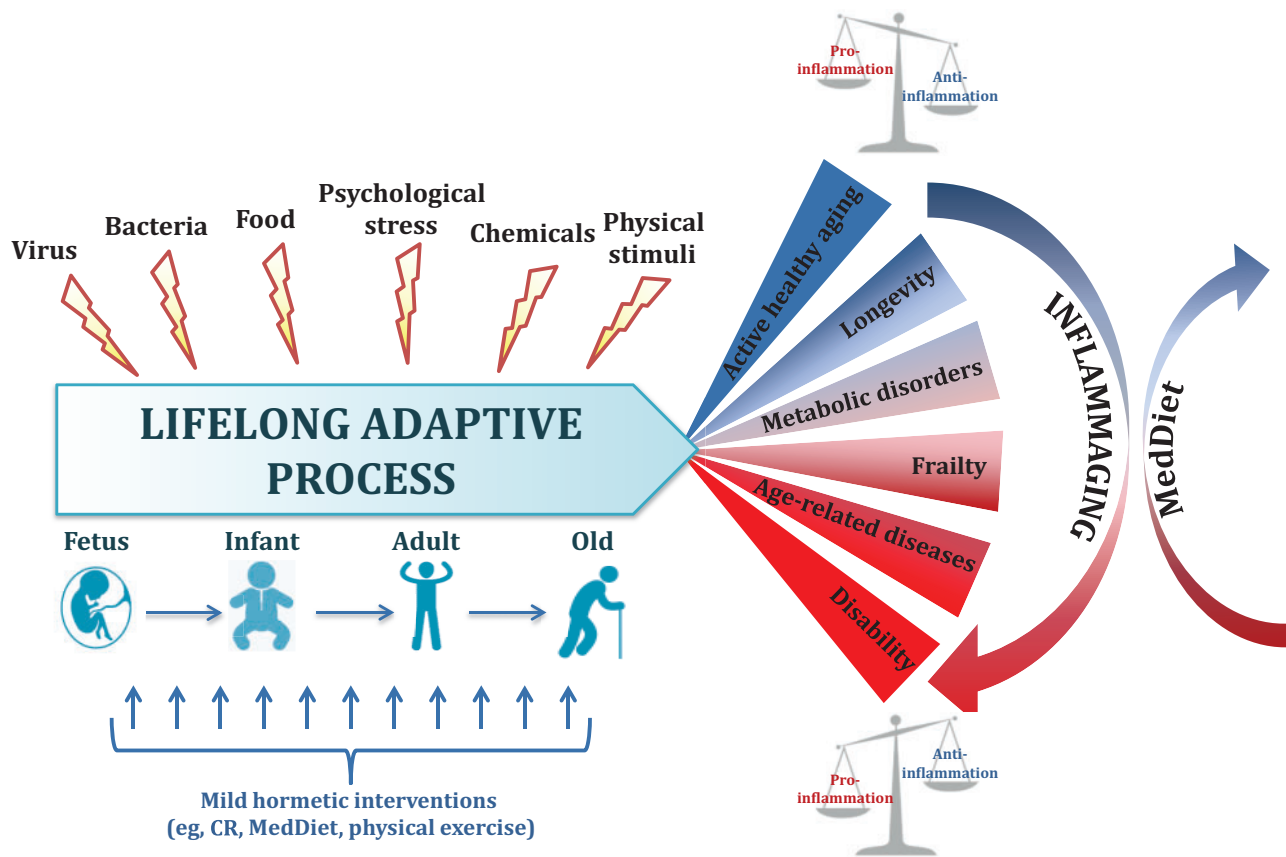


Figure 2 Aging as a lifelong adaptation to stressors. From intrauterine life to old age, humans are constantly exposed to a series of stressors that includes physical and chemical pollutants and viral and bacterial antigens, as well as food-derived molecules that are sensed by a series of stress-responding mechanisms, leading to a lifelong adaptation. Depending on the outcome of this adaptation, the balance between pro- and anti-inflammatory parameters may be preserved or not, and, consequently, aging will either be delayed or age-related diseases may emerge. The Mediterranean diet is a powerful tool to counteract inflammaging and its consequences. *Abbreviations:* CR, calorie restriction; MedDiet, Mediterranean diet.

NUCLEAR FACTOR ERYTHROID 2-RELATED VITAGENE NETWORK AND HORMESIS

Nuclear factor erythroid 2 (Nrf2) is a key transcription factor that regulates a wide range of genes (>500) with cytoprotective functions. The physiological activation of Nrf2 provokes a moderate stress response, ensuring health benefits and a prolonged lifespan in animal models.¹⁹ On the contrary, excessive long-term Nrf2 stimulation may lead to pathophysiological outcomes, classifying Nrf2 signaling as a hormetic-like pathway.^{20–24} One of the main networks regulated by Nrf2 is the vitagene system, a complex and integrated adaptive defense mechanism whose genes encode for members of the HSP family, such as heme-oxygenase-1 and HSP 72, thioredoxin/thioredoxin reductase, and sirtuins.^{25,26} The term *HSP* denotes a highly conserved cytoprotective mechanism that is devoted to protein folding and repair, but under no-stress conditions, is also involved in multiple functions such as transport of macromolecules, cell signaling, transcription, division, and

migration.^{27–29} Heme-oxygenase-1 (Hsp32), thioredoxin (a class of small redox proteins), and thioredoxin reductase can be transcriptionally upregulated by Nrf2 as part of the electrophile counterattack, also called the phase 2 response; this is a cell surveillance strategy to counteract any damaging effects of oxidant and electrophile molecules.^{26,30,31} The induction of a phase 2 response can lead to the expression of numerous Nrf2-dependent antioxidant genes,^{19,32,33} thus representing a strong mechanism for maintaining redox homeostasis. Sirtuins are a group of NAD⁺-dependent deacetylase enzymes involved in the regulation of vital biological processes such as apoptosis, cell differentiation, DNA repair, energy transduction, inflammation, and neuroprotection. They have, therefore, been associated with metabolic control, cell survival, and healthy aging.^{34–38} The vitagene network is a powerful system for the promotion of long-term health through an increase in cellular stress tolerance.^{39–41}

Among the activators of the vitagene system are several nutrients, including carnosic acid, resveratrol, sulforaphane, dimethyl fumarate, and acetyl-L-carnitine.^{31,37,42–47} This

supports the hypothesis that the beneficial effects of some nutrients are mediated through a hormetic stress response.

HORMESIS AND NUTRITION

The biphasic dose–response characteristic of the hormetic phenomenon can be triggered by multiple stressful conditions or toxic agents, including nutrients.^{37,41,48–50} Recent emerging evidence shows that vitamins, minerals, and phytochemicals may exert healthy benefits acting in a hormetic-like manner through the modulation of stress-response pathways, rendering the hormesis concept fully applicable to the field of nutrition.⁵¹ All of the compounds, natural or synthetic, that display this property are called hormetins.⁵²

Importantly, the activation of hormetic mechanisms in various animal models has appeared to prolong lifespan and delay the onset of age-related functional impairments.⁵³ It has been reported, for example, that calorie-restricted animals, which experience an extension of lifespan, show many signs of stress response and hypothalamic–pituitary–adrenal activation.⁵⁴ Thus, this type of nutritional intervention can be assumed to present a moderate amount of stress that is capable of inducing a hormetic response, thereby enhancing the ability of the organism to cope with many different noxae.⁵⁵ Nevertheless, it is interesting to note that the beneficial effect of calorie restriction is not universal but species specific⁵⁶ and that different mouse strains can have opposite responses, from life extending to life shortening,⁵⁷ suggesting that genetic background can play a major role in the control of stress response.

The MedDiet, one of the more intensely studied dietary patterns together with the Okinawan diet, is rich in foods containing mild (submicromolar) but significant concentrations of hormetins. Thus, it may be argued that the healthful features attributed to the MedDiet could, at least in part, be ascribed to a moderate and chronic activation of stress-response mechanisms due to the long-term consumption of low doses of these hormetins.

CULTURAL AND HEALTH SIGNIFICANCE OF THE MEDITERRANEAN DIET

The MedDiet is a cultural dietary model typically adhered to by populations living in the Mediterranean region. Some years ago, Keys et al.⁵⁸ demonstrated that Mediterranean populations, such as Greeks and Italians, showed reduced mortality from cardiovascular diseases compared with people living in northern Europe or the United States. Subsequently, several observational, longitudinal, and randomized controlled trials have demonstrated that the MedDiet may play a

role in the prevention of a wide range of chronic diseases, such as cardiovascular diseases, type 2 diabetes, cancer, and dementia, and could thereby reduce all causes of mortality.⁵⁹ These data were greeted with remarkable support by the international scientific community, fostering support for the diffusion of the MedDiet model as a tool to achieve an overall health condition that improves life expectancy. Thus, the MedDiet became one of the central pillars of public health policy programs in many countries.

The MedDiet has been included by UNESCO on its Representative List of Intangible Cultural Heritage of Humanity, which indicates it has exceptional scientific and cultural value. To be included on this list, it was determined that the diet met the following criteria: “Transmitted from generation to generation, particularly through families, the Mediterranean diet provides a sense of belonging and sharing and constitutes for those who live in the Mediterranean basin a marker of identity and a space for sharing and dialogue.”⁶⁰ UNESCO also determined that the MedDiet “could contribute to raising awareness of the significance of healthy and sustainable food related practices in other parts of the world, while encouraging intercultural dialogue, testifying to creativity and promoting respect for cultural, environmental, and biological diversity.”⁶⁰ The MedDiet is thus recognized not only as a diet but as a complete lifestyle based on the social and cultural aspects typical of Mediterranean countries.

To aid understanding of the MedDiet pattern, a dietary pyramid that provides a qualitative and quantitative graphical representation of the main food groups and their optimal consumption frequency was developed. This innovative graphical representation focuses on a global overview of the Mediterranean lifestyle, reflecting not only food selection, cooking, eating, and number of servings but also emphasizing details closely related to social and economic elements, such as the importance of regular physical activity, adequate rest, and conviviality.⁶¹ The MedDiet can be considered a recommended dietary pattern and a healthy and rewarding way of thinking, acting, and living.

EFFECT OF AN INTEGRATED STRESS RESPONSE STIMULATED BY THE MEDITERRANEAN DIET

The MedDiet is a well-balanced diet characterized by consistent intake of extra-virgin olive oil, vegetables, fruits, nuts and legumes, whole grains, and fish (especially marine species) and by moderate consumption of eggs, dairy products, lean meats, and alcohol (usually red wine during meals). At the same time, the MedDiet recommends a reduction of saturated fats (butter and

other animal fats), red meat, refined carbohydrates, and sweets (Box 1). On the whole, the MedDiet provides an equilibrated mix of nutrients with antioxidant, anti-inflammatory, and prebiotic effects (Figure 3). In addition, emerging experimental evidence, discussed herein, shows that some nutrients typical of the MedDiet, acting as hormetins, may elicit cellular stress responses (Table 1).

Phytochemicals

Phytochemicals (polyphenols, phytosterols, and carotenoids) are often considered as products without nutritive value. They constitute a heterogeneous group of bioactive compounds present in fruits, vegetables, nuts, grains, and legumes that display a strong anti-inflammatory function due to their powerful antioxidant profile. The antioxidant properties allow them to also exert an immunomodulatory and chemopreventive effect on cell regulatory activities. However, since the amount of phytochemicals normally consumed through diet is well below the micromolar order, the antioxidant effect of these molecules is not accounted for by a simple scavenging of reactive oxygen species. Recent studies suggest that this antioxidant action may be exerted by the activation of antioxidant stress responses (endogenous antioxidant enzymes, redox systems).^{25,62,63}

Evolutionarily, phytochemicals, which activate defense cellular stress-response pathways, have been developed by plants as a form of protection against pathogens, insects, and animals.^{26,47–49,64,65} Accordingly, the moderate and continuous consumption of phytochemicals through plant ingestion may induce hormetic responses.^{37,41}

Phytochemicals contained in the foods of a MedDiet and proposed as nutritional hormetins include ferulic acid, luteolin, phenethyl isothiocyanate, and resveratrol.⁴⁹

Ferulic acid. This is a phenolic compound abundant in fruit and vegetables such as tomatoes, sweet corn, and rice⁶⁶ which is able to promote the transcription of antioxidant genes, such as heme-oxygenase-1 and quinone oxidoreductase, through Nrf2 activation.⁴³ This compound also seems have a potential anti-inflammatory function, reducing levels of prostaglandin E2, tumor necrosis factor α , and nitric oxide synthase.^{67–69} It has also been reported to be efficient in combating colon carcinogenesis in rat,⁷⁰ skin tumorigenesis,⁷¹ and amyloid-beta peptide toxicity.⁷² Notably, high doses of ferulic acid induce mouse skin tumor promotion and oxidative stress,⁷³ whereas its derivatives display an effective capacity to suppress oxidative stress and inflammation at nanomolar concentrations, but not at the micromolar concentrations at which they become cytotoxic.⁷⁴

Box 1 Mediterranean diet in 9 points

1. High consumption of whole-grain cereals
2. High consumption of vegetables and fruit
3. High consumption of legumes
4. High consumption of fish
5. High intake of monounsaturated fatty acids (olive oil) and polyunsaturated fatty acids (fish, nuts)
6. Low intake of saturated fatty acids and hydrogenated oils
7. Low consumption of meat and meat products
8. Low-to-moderate consumption of milk and dairy products
9. Moderate consumption of alcohol (red wine at meals)

Luteolin. This is a flavonoid compound found in significant amounts in carrots, fennel, peppers, and celery. It has shown anticancer properties in a mouse model of skin tumor,⁷⁵ in human melanoma cells, and in human myeloid leukemia cells, where it induces cell cycle arrest or apoptotic cell death in a dose-dependent manner.^{76,77} In addition, luteolin may protect neuronal cell lines against oxidative damage induced by hydrogen peroxide⁷⁸ and counteract the toxic effects induced by *N*-methyl-4-phenyl-pyridinium.⁷⁹ These protective functions against oxidative stress depend on the activation of Nrf2.⁷⁹

Phenethyl isothiocyanate. This compound is found in crucifer vegetables such as turnips, watercress, and radishes, as well as in Chinese cabbage and rutabagas.^{80,81} The substance has been shown to exert a chemopreventive action in the case of mammary tumors and stomach and pulmonary adenomas, inhibiting the carcinogenesis induced by 7,12-dimethylbenz[a]anthracene in animal models.⁸² Phenethyl isothiocyanate also seems capable of preventing lung tumors induced by tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in rat and mouse.^{83,84} It may also induce apoptosis in human glioma cells,⁸⁵ oral cancer cells,⁸⁶ and human lung cancer cells.⁸⁷ Its remarkable chemopreventive action is likely due to the alteration of phase I/phase II enzymes that affect carcinogen metabolism.^{88,89} A recent paper reports its ability to protect human skin against ultraviolet radiation-induced oxidative stress and apoptosis through Nrf2 and antioxidant enzymes.⁹⁰

Resveratrol (trans-3, 5, 4'-trihydroxystilbene). This is a polyphenol that is present in >70 plant species and is particularly high in grapes (50–100 μ g of resveratrol per gram of fresh grape skin) and red wine. In plants such as *Vitis vinifera*, it is produced in response to infection (especially fungal) and to some environmental stresses

- Vitamins (B, C, E)
- “Good fats” (MUFA, PUFA)
- Polyphenols
- Phytosterols
- Carotenoids

- Legumes
- Unrefined carbohydrates

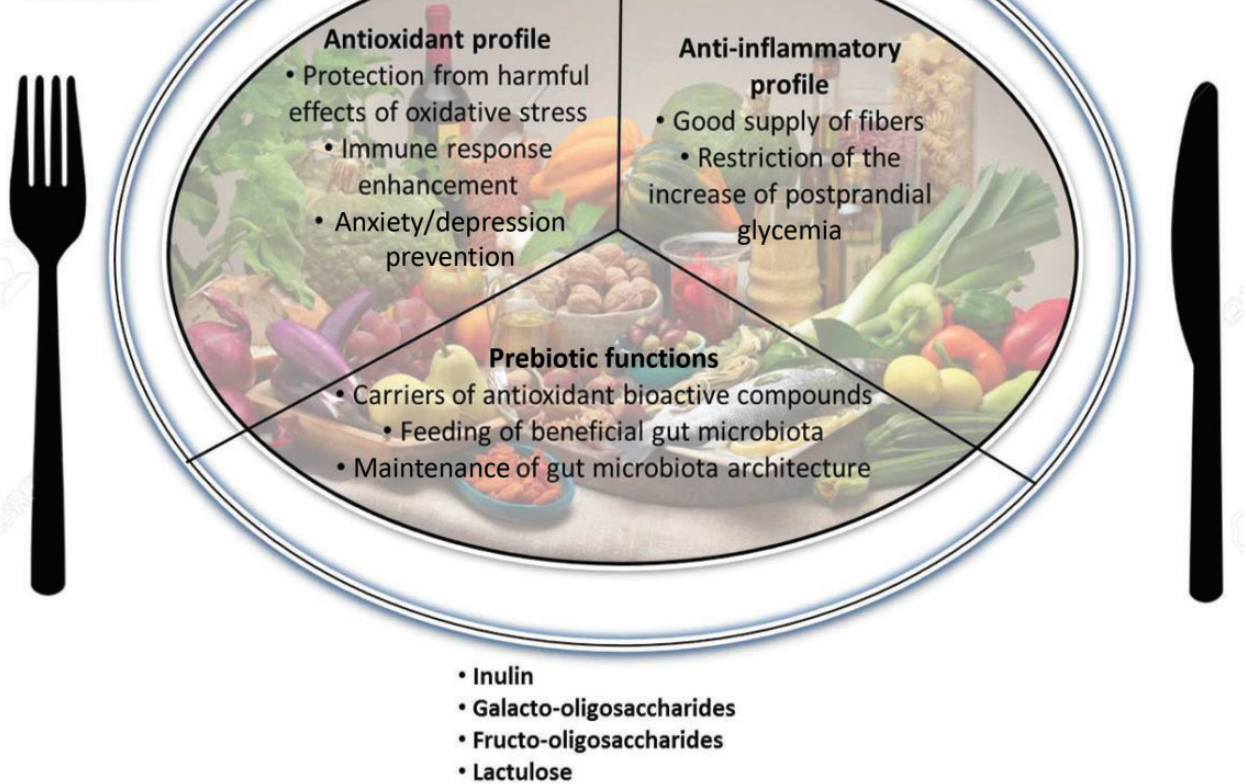


Figure 3 Beneficial components of the Mediterranean diet. Foods, nutrients, and micronutrients (ie, legumes, “good fats,” vitamins) provided by the Mediterranean diet contribute to its beneficial effects (antioxidant and anti-inflammatory profiles, prebiotic functions). *Abbreviations:* MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

Table 1 Nutritional hormetins of typical Mediterranean foods able to activate specific stress-response pathways

Nutritional hormetin	Food item within traditional Mediterranean diet	Stress pathway
Phytochemicals (phenolic antioxidants, terpenoids, carotenoids, and allium-derived sulfur compounds)	Olives, legumes, leafy green vegetables, tomatoes, eggplant, fruits, garlic, and onion	Activation of nuclear factor erythroid 2 (Nrf2)
Resveratrol	Grapes, red wine	Regulation of redox homeostasis Activation of Nrf2 and sirtuin pathway Blocking of nuclear factor κ B (NF- κ B)
Vitamin E	Dried fruits, herbs, leafy green vegetables	Activation of heat shock response Down-regulation of NF- κ B
n-3 polyunsaturated fatty acids	Fish, nuts	Activation of Nrf2 Blocking of NF- κ B
Fiber	Legumes, unrefined whole-grain cereals, fresh vegetables, fruits	Cooperation with cellular stress pathways (heat shock proteins)

(ie, water deprivation and ultraviolet irradiation) and acts as a natural antibiotic as well as an inhibitor of proliferation.⁹¹ Given its ability to scavenge intracellular radical oxygen species, resveratrol is considered a potent natural in vivo antioxidant.⁹² However, like most antioxidants, resveratrol can effectively scavenge free

radicals if present at micromolar concentrations. Bioavailability studies have shown that resveratrol is quickly absorbed in the gastrointestinal tract after oral consumption, but it is metabolized in its glucuronide and sulfate derivatives by rapid metabolism in enterocytes. Thus, the blood concentrations of resveratrol are

in the nanomolar range, making it almost impossible to reach pharmacologically significant doses.^{93,94} It has, therefore, been suggested that its positive effects are mediated by a hormetic mechanism.^{95,96} In this regard, resveratrol has been demonstrated to be a potent allosteric activator of SIRT1,⁹⁷ a member of the sirtuin family able to mediate the healthy benefits of dietary restriction and physical exercise.⁹⁸ For this reason, resveratrol has been indicated as an effective mimetic of some of the effects of calorie restriction.⁹⁹ In addition, resveratrol can induce the activation of the Nrf2 pathway and the inhibition of nuclear factor κ B (NF- κ B) activity,^{100–102} exerting a protective effect against neuroinflammation and counteracting the progression of brain aging. The mechanism of action of resveratrol can be represented by a biphasic dose–response curve where low doses of this phytochemical induce mild stress in neural cells, enhancing the ability of the nervous system to cope with stress and promoting its optimal function and longevity.¹⁰³ Until now, only a few clinical trials evaluating the potential therapeutic outcomes of resveratrol have been performed, with quite discordant results.¹⁰⁴ A meta-analysis of 11 studies indicated that resveratrol consumption significantly reduces fasting glucose, insulin, glycated hemoglobin levels, and insulin resistance in diabetic participants, whereas it has no effect on the glycemic profile of nondiabetic persons.¹⁰⁵ However, a more recent randomized, double-blind, crossover study has demonstrated that resveratrol supplementation did not improve hepatic or peripheral insulin sensitivity in subjects with well-controlled type 2 diabetes.¹⁰⁶ An active grape formulation containing polyphenols that was administered for 6 months to elderly subjects with mild cognitive impairment prevented brain metabolism decline in the right posterior cingulate cortex and in the left superior posterolateral temporal cortex. Even if no significant differences with respect to the placebo group were found in the neuropsychological battery scores, a protective effect of grapes against the early pathologic metabolic decline typical of Alzheimer's disease has been hypothesized.¹⁰⁷ In summary, resveratrol can be considered a nutritional phytochemical hormetin able to elicit adaptive stress-response signaling pathways that increase cellular resistance to injuries and diseases.

On the whole, some plant polyphenols, which are abundantly present in the MedDiet, may exert positive modulations on health and lifespan through the activation of metabolic responses and stress-related pathways similar to the responses elicited by calorie restriction and intermittent fasting.¹⁰⁸

Besides the above-mentioned specific substances, phytochemicals such as phenolic antioxidants, terpenoids, carotenoids, and allium-derived sulfur compounds, which are commonly present in traditional foods of the MedDiet

(olives, legumes, leafy green vegetables, tomatoes, eggplant, fruits, garlic, and onion), are capable of inducing the stress response through Nrf2.^{109–113}

Furthermore, oleuropein, curcumin,¹¹⁴ and quercetin are able to control the oxidative stress load by activating the ubiquitin-proteasome system or Nrf2, which leads to the transcription of proteasome subunit genes.^{115,116} The ubiquitin-proteasome system is one of the main intracellular protein degradation machineries and is devoted to the clearance of short-lived regulatory protein and the removal of misfolded, damaged, and oxidized proteins,^{117–119} thus representing a key mechanism in cellular homeostasis maintenance.

Vitamins

Appropriate daily doses of vitamins are essential and beneficial, whereas their excess can lead to hypervitaminosis, following a hormetic U-shaped curve.^{120,121} Vitamins directly activate cellular and systemic pathways to serve as defense mechanisms against different stressors.¹²² The A, C, and E vitamins, which display free-radical scavenging features, are discussed here briefly because redox homeostasis is a fundamental goal of stress responses.

Vitamin A. This vitamin and its active derivatives (retinoids) are key players in many physiological processes such as eyesight, reproduction, embryonic growth and development, immune competence, cell differentiation and proliferation, apoptosis, maintenance of epithelial tissue, and brain functions. Carotenoids, the precursors of vitamin A, are fruit and vegetable pigments with several properties. They are immunostimulants, they exert photoprotection of sunlight-exposed tissues,¹²³ they prevent oxidative tissue damage, and they modulate the Nrf2 signaling pathway. Thus, typical Mediterranean foods rich in carotenoids, such as tomatoes and leafy green vegetables, may also be considered Nrf2 activator foods.¹⁹

Vitamin C. This vitamin is mainly found in fresh fruits (including citrus fruits, berries, kiwi) and vegetables (including brassicas, peppers, leafy greens, tomatoes). Its antioxidant activity is needed for tissue growth and repair and to block the oxidative damage caused by cancer, heart diseases, and other pathological conditions.¹²⁴ An increase in the daily intake of vitamin C is recommended in cases of infections, surgical procedures, cigarette smoking, other stress-related conditions, and diets poor in fresh plant food and fruit.¹²⁵

Vitamin E. This vitamin is contained especially in dried fruits, herbs, and leafy green vegetables. It preserves cell membranes from free-radical activity and is one of the most effective nutrients for strengthening the immune

system. Several studies in animal and human models have shown that vitamin E deficiency impairs the humoral and cell-mediated immune function; conversely, its supplementation reinforces the immune response against several pathogens, thus accelerating infection resolution, particularly in elderly people.¹²⁶ A recent study performed on sheep showed that dietary antioxidant supplementation with vitamin E plus selenium may protect against heat stress by inducing the expression of skeletal muscle HSP70 and HSP90 and the downregulation of NF- κ B.¹²⁷ The HSPs represent a highly conserved cytoprotective mechanism essential for cell survival, whereas NF- κ B is the crucial transcription factor responsible for the proinflammatory response to stress.¹²⁸ In addition, different isoforms of vitamin E (α -, γ -, δ -tocopherol) have been shown to be involved in the activation of Nrf2 and NF- κ B pathways, thus modulating the inflammatory response in human intestinal cells.¹²⁹

Lipids

The so-called “good fats” are the monounsaturated fatty acids and polyunsaturated fatty acids (PUFAs) found in vegetable oils (especially extra-virgin olive oil), nuts, seeds, and fish. The MedDiet provides an excellent dietary fat profile characterized by a low intake of saturated fats and trans-fatty acids¹³⁰ and an optimal ratio between n-6 and n-3 PUFAs. This fat combination and proportion in the MedDiet provides this dietary pattern with one of the most powerful anti-inflammatory profiles. Animal studies suggest that dietary supplementation with n-3 PUFAs prevents anxiety and depressive behavior, as well as stress-induced learning/memory deficits.¹³¹ In humans, n-3 PUFAs have also been found to exert antidepressive and antistress effects.^{132–134,135} A meta-analysis confirmed that n-3 PUFA levels are lower in depressed patients compared with control subjects, whereas no differences in n-6 PUFAs levels were observed. Of the 2 most prevalent n-3 PUFAs, eicosapentaenoic acid (EPA) seems to be more effective than docosahexaenoic acid (DHA) in treating depression symptoms.^{133,136} Concerning physiological responses to stress, 3 weeks of supplementation with n-3 PUFAs (fish oil) significantly reduced plasma levels of cortisol, adrenaline, and nonesterified fatty acids, as well as energy consumption elicited by mental stress effects in health conditions.¹³⁵ Intake of n-3 PUFAs can also influence mood and cognition by blocking the NF- κ B pathway,^{137,138} thus protecting against proinflammatory stress responses.¹²⁸ Frequent consumption of marine fish, which is typical with a MedDiet, provides high levels of EPA and DHA competing with n-6 PUFAs for the same series of enzymes; this reduces the production

of arachidonic acid-derived proinflammatory eicosanoids, such as prostaglandin E2, leukotriene B4, and thromboxane (2-series), with a chemotactic and procoagulant action, and increases the synthesis of anti-inflammatory eicosanoids, such as prostaglandin E3, leukotriene B5, and thromboxane (3-series), with immunomodulatory and neuroprotective effects.¹³⁹ Furthermore, moderate concentrations of DHA and EPA, alone or in combination, activate the Nrf2 pathway and the mRNA expression of its target genes, achieving optimal antioxidant cellular protection.¹⁴⁰

The specific properties of olive oil are described in [Box 2](#). This dietary product is a mix of various chemical compounds and can be considered one of the iconic foods of the MedDiet, together with red wine.

Carbohydrates and fiber

The most common carbohydrate-rich foods in the MedDiet are nonrefined whole-grain cereals and legumes. Legumes are low-fat, nutrient-rich foods that provide large amounts of vitamins, minerals (iron, selenium, phosphorus, and potassium), protein, and fiber. The consumption of both whole-grain cereals and legumes has the advantage of reducing the increase of postprandial glycemia and ensures a good supply of dietary fiber. Indeed, low glycemic indexes help to keep the postprandial rise of blood glucose levels and, consequently, insulin secretion under control. It has been demonstrated that high insulin levels foster inflammation,¹⁵⁵ and the consumption of high-glycemic-index foods is associated with increased cardiovascular risk. On the other hand, low-glycemic-index diets have antiatherogenic effects because they lead to a decrease in the production of atherogenic lipoproteins, oxidized low-density lipoproteins, and inflammatory biomarkers (C-reactive protein, plasminogen activator inhibitor-1).¹⁵⁶ In addition, these foods play a very important role in preventing hypercholesterolemia and type 2 diabetes.¹⁵⁷ Interestingly, metabolic dysfunctions seem to also be regulated by intracellular stress pathways. For example, HSP90 inhibitors may improve the regulation of glucose metabolism in diabetic mice,¹⁵⁸ whereas decreased expression of HSP72 in skeletal muscle of patients with type 2 diabetes correlates with insulin resistance.¹⁵⁹ These and other types of emerging experimental evidence suggest that stress-response mechanisms, metabolic pathways, and nutrients may jointly regulate metabolic functions at cellular and physiological levels.¹⁵⁸ Therefore, a dietary pattern generating a low glycemic load, like the MedDiet, may protect against metabolic dysfunctions and also cooperate with stress-response pathways.

Box 2 Properties of olive oil

- Olive oil represents the main source of fat in the Mediterranean diet. The health-promoting effects of olive oil have been described relative to the prevention of several conditions, such as cancer, metabolic syndrome, cardiovascular and cerebrovascular events, neurodegenerative diseases, and autoimmune inflammatory diseases.^{141–144}
- Extra virgin olive oil (EVOO) is obtained from olives exclusively by mechanical or physical methods, under conditions that do not modify its natural composition. Oleic acid (18:1, n-9) is the most represented fatty acid (FA) (36%–84% of the FA total fraction), whereas linoleic acid is the main essential polyunsaturated fatty acid (3%–21% of the FA total fraction) in EVOO. In particular, oleic acid has the following cardioprotective benefits: affects plasma lipids and lipoprotein patterns; affects blood cell membrane composition and fluidity; inhibits coagulation; improves glucose metabolism; controls blood pressure; and modulates inflammation and oxidative stress.¹⁴⁴
- Besides its excellent lipid profile, EVOO contains hundreds of bioactive compounds, including a number of triterpens (ie, squalene), biophenols (phenyl alcohols hydroxytyrosol, tyrosol, oleuropein, ligstroside, verbascoside, lignans, flavonoids), pigments (chlorophylls and carotenoids, xanthophylls, lutein), and vitamin E (tocopherols), which several studies have indicated are responsible for the beneficial effects of EVOO.^{145–147} The antioxidant, antimicrobial, and anti-inflammatory properties of these molecules, as well as their effects on lipid metabolism, were recently reviewed.¹⁴⁴ Given that the antioxidant activity of EVOO biophenols in vivo is critically restricted by their low bioavailability, their systemic positive effects are likely due to activation of the endogenous stress-response systems (drug-metabolizing enzymes, antioxidant and phase II enzymes, and transporter proteins).¹⁴⁸ Thus, it can be suggested that EVOO biophenols could function as hormetic compounds that are able to trigger adaptive response pathways (parahormesis).¹⁴⁹ The low level of oxidized forms of EVOO biophenols in plasma and tissues can transiently induce a mild state of oxidative stress capable of upregulating the endogenous antioxidant and detoxification enzymes and of rendering the cell more resistant against the long-term damaging effects of more powerful oxidative stress stimuli. In particular, the positive hormetic effect of EVOO biophenols at their low in vivo concentration may be exerted through the activation of the Nrf2-targeted “early warning signal.”¹⁴⁸ In fact, a number of recent studies have shown that hydroxytyrosol, oleuropein, and oleacein can activate the Nrf2 pathway both in in vitro cellular models^{150–152} and in vivo animal models.¹⁵³ In addition, the anticancer activity of EVOO secoiridoids (oleuropein aglycon and decarboxymethyl oleuropein aglycon) is related to the activation of antiaging/cellular stress-like gene signatures (endoplasmic reticulum stress, sirtuin-1, NRF2 signaling, and the energy-sensing protein AMPK, a critical gerosuppressor of mTOR).¹⁵⁴

In addition, the weekly consumption of whole-grain cereals and legumes suggested by the MedDiet provides a good amount of dietary fiber (β -glucans, arabinoxylans, galactomannans, pectins) with numerous advantages for the consumer. In fact, fiber helps to achieve satiety and control body weight, while exerting a proven anti-inflammatory action that decreases systemic inflammation-associated biomarkers, such as C-reactive protein, interleukin 6, and tumor necrosis factor α ,^{160–162} and inhibits the expression of specific inflammation-related genes such as cyclo-oxygenase-2 and inducible nitric oxide synthase.¹⁶³ Fiber is also an efficient carrier for antioxidant bioactive substances like vitamins, carotenoids, and polyphenols, which follow a common and synergic physiological process within the gastrointestinal tract.

Specific dietary fibers called prebiotics (eg, inulin, galacto-oligosaccharides, lactulose, fructo-oligosaccharides), which are contained in plants, cereals, fresh and dried fruits (particularly bananas, onions, garlic, asparagus, wheat, rye, Jerusalem artichoke), and legumes,¹⁶⁴ have a central role in the maintenance of gut health, as they provide the selective substrate for the growth of “health-promoting bacteria” such as *Bifidobacterium* and *Lactobacillum*.¹⁶⁵

Overall, these micronutrients (phytochemicals, vitamins, fats, complex carbohydrates, and fibers) may exert multiple positive effects on human health. All of

the data reported above seem to indicate that the healthful properties of the MedDiet could be partially accounted for by a hormetic stress response elicited by these compounds (Table 1). Indeed, when consumed in excess, many of these nutritional hormetins become detrimental, exerting a dual effect that fits perfectly with the biphasic curve of the hormetic response.

NEUROHORMESIS AND THE GUT–GUT MICROBIOTA–BRAIN AXIS

Phytochemicals found in fruit and vegetables exhibit several neuroprotective properties. Various interventional trials suggest that a diet rich in phytochemicals may enhance neuroplasticity and resistance to neurodegeneration, thereby postponing or preventing neurodegenerative disorders, including Alzheimer’s and Parkinson’s diseases in animal models.^{25,48,166} The term *neurohormesis* indicates the ability of the central nervous system to respond to exogenous as well as endogenous (ie, nitric oxide, carbon monoxide, glutamate, Ca^{2+}) toxic agents,^{167–170} which represent mild stress and a driving force to augment the neuronal resistance toward stronger insults.²⁵ There are several examples of neurohormetic phytochemicals, such as curcumin, sulforaphane in broccoli, and other chemical compounds contained in blueberry, green tea, green leafy vegetables, citrus fruits, coffee, and dark chocolate.^{25,49}

Garlic and onion are rich in volatile organosulfur substances, such as allium and allicin, capable of inducing the Nrf2 pathway.^{62,171} Among them, diallyl trisulfide has been shown, in rat spinal cord explants, to protect motor neurons against glutamate-induced excitotoxicity by activating Nrf2 and increasing the expression of the antioxidant enzyme quinone oxidoreductase 1.¹⁷² Other allyl-containing sulfides might upregulate neuroprotective mitochondrial proteins activating stress-response mechanisms.¹⁷¹

Carnosic acid is abundant in rosemary (*Rosmarinus officinalis*), which is a very common herb in the Mediterranean basin¹⁷³ and an acknowledged inducer of Nrf2.^{174,175} Carnosic acid has been demonstrated to protect against ischemia and reperfusion by activating phase 2 enzymes and reduced glutathione (GSH) metabolism in mouse brain.¹⁷⁴ This function has been confirmed by another study performed in murine hippocampal cells.¹⁷⁶ In addition, carnosic acid may enhance the expression of neurotrophin nerve growth factor, promoting neurite outgrowth in neuronal culture cells.¹⁷⁷ A similar mechanism dependent on Nrf2 has also been detected in normal human astrocytes.¹⁷⁵

Caffeine is a well-known psychoactive substance widely consumed worldwide. Recent investigations highlighted the role of caffeine in improving cognitive functions and synaptic plasticity and in counteracting neurodegeneration in Alzheimer's and Parkinson's diseases.^{178–180}

Ferulic acid ethyl ester, a hydrophobic form of ferulic acid, may increase heme-oxygenase activity in rat astrocytes/neurons¹⁸¹ and may protect against oxidative stress induced by amyloid-beta peptide on isolated synaptosomes (synaptic terminal from neurons).¹⁸²

Resveratrol also displays neurohormetic functions, as detailed above in the section on phytochemicals.

Finally, in the study of the relationship between diet and the central nervous system, the central role of gut microbiota and its influence on neurological and psychological pathways, cognition, and behavior is emerging.¹⁸³ The gastrointestinal tract and the gut microbiota establish a strong bidirectional connection with the central nervous system (gut–gut microbiota–brain axis), integrating the neurohumoral signals from/to the central nervous system, the neuroendocrine and immune systems, the autonomic nervous system, and the enteric nervous system.¹⁸⁴ A number of experimental observations have shown that even mild alterations of gut microbiota composition are able to provoke modifications of cerebral functions, and, vice versa, the brain can deeply affect intestinal functions through the secretion of hormones, neuropeptides, and neurotransmitters (substance P, neurotensin, corticotropin-releasing factor, 5-hydroxytryptamine,

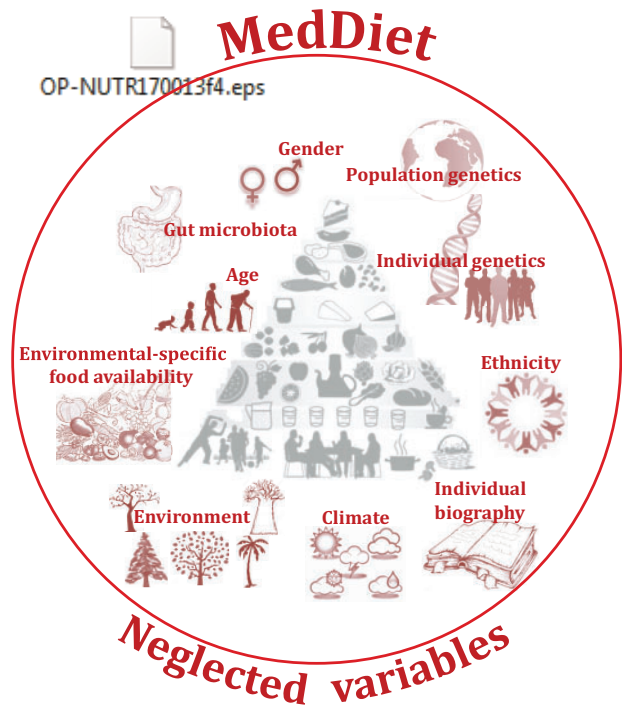


Figure 4 Critical and neglected aspects of the Mediterranean diet's effect across individual, population, and environmental variables within a global perspective. Abbreviation: MedDiet, Mediterranean diet.

and acetylcholine).¹⁸⁴ Microbial subproducts may cross-react with human antigens and stimulate the immune system,^{185,186} and neurotoxic metabolites (such as D-lactic acid and ammonia) are able to cross the blood–brain barrier and cause neurotoxicity or neuroinflammation.^{187–189}

THE EUROPEAN NU-AGE PROJECT

One of the main goals of the recently concluded European Commission–funded project NU-AGE (“New dietary strategies addressing the specific needs of the elderly population for healthy aging in Europe”; grant agreement 266486, www.nu-age.eu),^{190,191} whose results are currently being processed, was to test the hypothesis that inflammaging can be counteracted by a complete MedDiet-based nutritional approach suitably customized for different elderly populations in Europe (NU-AGE diet)¹⁹² as well as the importance of crucial but neglected aspects impacting MedDiet efficacy (Figure 4). Within this framework, 1250 volunteers, aged 65–79 years and gender-balanced, were enrolled in 5 European countries (Italy, France, Poland, the Netherlands, and the United Kingdom). At the beginning and end of the 1-year NU-AGE diet trial, all subjects underwent a comprehensive evaluation concerning genetics, epigenetics, transcriptomics,

metagenomics, and metabolomics. The particular approach of the NU-AGE project might make it possible to not only identify a greater number of molecular processes involved in the dietary response to inflammaging but also to study the possible hormetic effects of the MedDiet components.¹⁹³ Further studies like NU-AGE are necessary to disentangle the complex network of cellular pathways regulated by the MedDiet and its hormetic properties and to evaluate the impact of individual, population, and environmental variables on different outcomes such as age-related diseases, aging, and longevity.

CONCLUSION

The finds of this review suggest that, on the basis of available experimental evidence, the well-recognized epidemiological beneficial outcomes of the MedDiet can be likely ascribed to a long-lasting hormetic effect. The data summarized here indicate that a variety of hormetins present in foods, mostly of vegetal origin, are a characteristic and important component of the MedDiet. The conceptualization of the MedDiet as a hormetic intervention fits the emerging general hypothesis that the most effective antiaging interventions, capable of largely preventing and/or postponing age-related pathological conditions, act by promoting hormetic effects. Indeed, the 2 most feasible and effective antiaging pillars, ie, nutritional intervention (calorie restriction and intermittent fasting) and appropriate physical activity, have been interpreted within the hormesis paradigm. Both types of hormetic intervention have been shown to decrease the accumulation of senescent cells, which largely contribute to inflammaging with their proinflammatory secretory phenotype,¹⁹⁴ thus attenuating age-related deterioration and preserving the functionality of several organs. The findings of this review support the previously reported suggestion¹⁹⁵ that a moderate level of stressors may be determinative in setting the basal tone of stress resistance mechanisms, thereby maintaining and preserving the health status.

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