

## **Mediterranean Diet and Health Promotion: evidence and current concerns**

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### **Abstract**

The Mediterranean diet (MD) is a dietary pattern described by Ancel B. Keys in the 1950s as a typical dietary habit of some populations bordering the Mediterranean sea in the south of Europe characterized by frugal living style. Findings of the Seven Country Study showed that people faced in the Mediterranean area had a reduced incidence of cardiovascular and metabolic disease, cancer and age-related diseases. The mechanisms through which the MD exerts its health benefit and prevents the onset of several diseases are not completely clarified because of various and complex aspects. Several studies suggest that the claimed benefits of the MD dietary pattern is mainly linked to decreased inflammation and oxidative stress, strongly related to each other and involved in many chronic diseases. The high content of compounds with antioxidant and anti-inflammatory activity present in most foods of the MD pattern has been considered effective for the improvement of many functions and parameters, therefore useful for the maintenance of the health status and the prevention of many chronic diseases. However, the extensive metabolism to which antioxidant compounds are subjected, once ingested with foods, reduces their antioxidant activity within the systemic circulation and tissues and their concentrations are very low in comparison with endogenous antioxidants. Foods produced for human nutrition have significant consequences for both the environment and the health of a specific population, and, in turn, the environment may address food choices and affect eating habit. The MD is a sustainable diet model that presents a very low environmental footprint, promotes the bio-diversity and protects human health and well-being. However, we must not ignore the planet changes and global environmental aspects that might convert the MD into a theoretical eating model far away from that described by Keys.

## 1. Introduction

Strong evidence highlights profound lifestyle changes of the world's population as a consequence of global socio-economic shifts, evident even in low- and middle-income developing countries (Traill et al. 2014, Fazel-Tabar Malekshah et al. 2016, Mehio Sibai et al. 2010, Fuster & Kelly 2010, Schwingshackl & Hoffmann 2015). Several studies (Loef & Walach 2012, van Dam et al. 2008, Khaw et al. 2008) showed that modern food production/distribution and increased industrialization of agro-food systems have influenced significantly the worldwide dietary habit and nutritional components of eating patterns with a strong impact on nutritional outcomes (Owolabi et al. 2016, World Health Organization 2011, Hawkes 2006, Garnett et al. 2013, Knight et al. 2016). It is widely demonstrated that eating habit as a whole, rather than an individual nutrient or groups of them, interacts with health status (Schulze & Hu 2002, Jacques & Tucker 2001, Fung et al. 2001) and may have a significant influence on modifiable risk factors of non-communicable diseases (NCDs), which are reaching epidemic proportions worldwide. The consumption of high-caloric obesogenic foods, endemic to industrialized nations and increased in the developing countries on which economic growth and globalization have triggered the phenomenon known as “nutrition transition” (Belahsen 2014, Gayathri et al. 2016), caused a progressive abandon of traditional diet patterns and has determined, at the same time, a very frequent adoption of unhealthy eating habit so increasing the susceptibility to the onset of diet-related chronic diseases (Hawkes 2006). Conversely, as recently observed, dietary behaviour should not disregard the use of local foods which are naturally cultivated in a specific geographic region and comply with important ecological, economic and cultural aspects (Lacoppidan et al. 2015, Gayathri et al. 2016, Iriti & Vitalini 2012). It is well known that habitual

consumption of foods high in fats and sweeteners may contribute significantly to the onset of NCDs by increasing the burden of multiple risk factors such as inflammation, hypertension, hyperglycemia, dyslipidemia and obesity (Menotti et al 2012, Schwingshackl & Hoffmann 2015). Instead, high compliance to healthy diets, as assessed by validated tools/scales evaluating diet quality (Donini et al. 2016, Schwingshackl & Hoffmann 2015, Mertens et al. 2017) is positively linked with longevity, may interfere on all-cause mortality and lower the risk for developing cardiovascular events (CVD) and stroke, cancer and neurodegenerative disease (World Health Organization 2003, Chiuve et al. 2012, Harmon et al. 2015). There is no doubt that aging-associated diseases are currently and will continue to be a worldwide public health burden in the near future. Unhealthy dietary habit by increasing the susceptibility to age-dependent inflammation and oxidative stress (Di Massimo et al. 2006, Castellani et al. 2016) amplifies the burden of the risk factors in the onset of NCDs. Therefore, the world challenge for the immediate future is promoting human health on a planet where the global life expectancy and the spread of diseases linked to unhealthy diets are increasing and planet resources undergo a progressive depletion. It is known that an adequate, well balanced diet combined with regular physical activity is a cornerstone of good health status and that nutrition interferes positively with the individual disease risk profile at both primary and secondary level of prevention (Gostin et al. 2017, Kones 2011, Lloyd-Jones et al. 2009, Lloyd-Jones et al. 2010, Reedy et al. 2014). The 2013 World Health Assembly endorsed the Global Action Plan on Non-communicable Diseases 2013–2020 “*which proposed a sustainable set of actions for Member States, international partners and the WHO Secretariat to prevent NCDs, promote healthy diets and physical activity,*

*and to attain the nine voluntary global NCD targets by 2025. The nine targets include halting the rise in diabetes and obesity in adults and adolescents as well as the increase of childhood overweight and obesity by 2025”* (World Health Organization 2014). On the basis of scientific evidence and thematic areas on health promotion in the world's population, measures and interventions have been developed in numerous countries to develop effective strategies according to food-based dietary guidelines and validated dietary indexes and with the aim of reducing the risk burden related to unhealthy dietary patterns (Schwingshackl & Hoffmann 2015, World Health Organization 2003, Wirt & Collins 2009, Watson et al. 2010). In a large case-control study of acute myocardial infarction (AMI) showing the association between dietary patterns and a dietary risk score with AMI and in different regions of the world (Iqbal et al. 2008), western, prudent and oriental dietary patterns have been considered. The western dietary habit, characterized by fried foods, salty snacks, eggs, and meat, was associated with an increased risk for CVD in all countries of the world; the oriental pattern, high in intake of tofu and soy, showed no relationship with AMI risk, whereas the prudent pattern, high in fruits and vegetables, was associated with a lower CVD risk. Therefore, the increased consumption of vegetables and fruits may have the potential for lower incidence and mortality from CVD. The adoption of a Mediterranean-type diet which is characterized by a high consumption of vegetables and fruits, confirms its health value by favouring many beneficial outcomes and justifies its effectiveness in decreasing the risk for the most important chronic diseases (Lairon 2007, Fung et al. 2009, Sofi et al. 2008).

The present study provides an overview of the evidence on healthy effect of Mediterranean diet (MD) and on some

aspects which may limit and interfere with its beneficial characteristics.

## **2. The Mediterranean Diet: the scientific evidence on health promotion**

As well known, the traditional MD is a dietary pattern described by Ancel B. Keys in the years 50-60 of the last century as a typical, simple eating habit of some populations bordering the Mediterranean sea accustomed to a frugal living style due to the severe economic crisis following the Second World War and a low technology level (Keys et al. 1986, De Lorgeril et al. 1999, World Heart Organization Study Group 1990). The results of the Seven Country Study, legendary in the field of medicine, showed that people faced in the Mediterranean area, compared with the other populations analyzed in the study, had a reduced incidence of cardiovascular disease and a lower degree of meta-inflammation, which, as known, is an important feature of the aging process and age-related diseases (Keys et al. 1986, Di Massimo et al. 2006, Starr et al. 2009). The scientific research has largely confirmed the health-promoting effects of the MD highlighted by the pioneer Seven Country Study (Vareiro et al. 2009, Bach-Faig et al. 2011), and additional positive effects of the MD for maintaining the health status have been also observed for diseases other than CVD such as cognitive impairment, depression, and neurodegenerative diseases (Knight et al. 2016, Reedy et al. 2014, Sofi et al. 2008, Psaltopoulou et al. 2013, Psaltopoulou et al. 2008). Previous studies showed that a high adherence to the MD pattern may be associated with an improvement of endothelial function and to decreased plasma levels of inflammatory and oxidative stress markers, known to be involved as mediators of several diseases (Vogel et al. 2000, Medina-Remón et al. 2017, Calcabrini et al. 2017, Ciancarelli et al. 2016). Interestingly, evidence was provided that a two point increase in the

score for adherence to the MD is sufficient to reduce the incidence of Parkinson's and Alzheimer's disease (Sofi et al. 2008). The MD patterns differ among the countries bordering the Mediterranean sea because of a variety of typical socio-cultural traditions, agricultural production and economy (Dernini & Berry 2015, Noah & Truswell 2001), but some common and specific features may be individualized. High consumption of seasonal fruit and vegetables, whole cereals and legumes, moderate/very low intake of dairies and animal products are common eating habit of Mediterranean populations devoted mainly in the past to agricultural work (Keys et al. 1986, Knooks et al. 2004, Sofi et al. 2014). Remarkably, the main source of dietary fat is represented by extra-virgin olive oil. Globally, the MD is rich in monounsaturated fatty acids, primarily oleic acid, dietary fibers, antioxidant compounds such as polyphenols, and a high ratio of omega-3 to omega-6 polyunsaturated fatty acids (Medina-Remón et al. 2017). Core components of traditional MD are also aromatic herbs and spices, that seem to increase the healthy characteristics of this virtuosos eating habit (Keys et al. 1986, Vallverdú-Queralt et al. 2014, Bower et al. 2016), regular but moderate red wine consumption often consumed with meals, food palatability/preparation and, as elegantly observed by Iriti & Vitalini (2012), *“eating together around the same table: ‘we do not sit at table to eat, but to eat together’ (Plutarch) (UNESCO nomination file n. 00394)”*. Indeed, the MD, intangible heritage of humanity, is not a banal list of foods with different potential on health promotion but it is a complex model of eating pattern unquestionably integrated with the culture, lifestyle, tradition, family ties, and social relations. In the Ikaria Study, the percentage of people over the age of 90 years living in the Greek island of Ikaria was much higher than the European population average. The majority of the subjects

observed regular physical activity, healthy eating habits (avoidance of smoking and spirits, very low consumption of wine during meals), midday naps, frequent socializing, thereby showing that the link between virtuous lifestyle, frugal eating behaviour and the observance of traditions may favourably influence the aging process and life expectation (Panagiotakos et al. 2011). So far, the mechanisms of action through which the MD exerts its health benefit as a whole and prevents the onset of several diseases are not completely clarified because of various and complex aspects. Most of the studies identifying the possible mechanism by which the MD plays its beneficial potential have been carried out by assessing single nutrients or food groups. The results seem to confirm a significant relationship between the consumption of determined foods and a possible prevention of cardiovascular disease, diabetes, and cancer (Oliviero et al. 2015, McKay et al. 2010, Medina-Remón et al. 2017, Calcabrini et al. 2017, Korre et al. 2014). Large observational studies and randomized trials support that the claimed benefits of the MD pattern or of the consumption alone of its characterizing foods is mainly linked to reducing the impact of inflammation and oxidative stress which are strongly related to each other and are involved in the aging process and in a number of chronic diseases including diabetes, cardiovascular and neurodegenerative diseases, and cancer (Halliwell & Gutteridge 1999, Medina-Remón et al 2017, Kolovery et al. 2016, Davis et al. 2017, Hernáez et al. 2017, Chrysohoou et al. 2004, Esposito et al. 2004, Colomer & Menéndez 2006). Both nutritive and non-nutritive components of the MD show significant anti-inflammatory activities which influence the arachidonic acid cascade, the expression of some proinflammatory genes, and the activity of immune cells (Preedy & Watson 2015). Moreover, the high antioxidant potential due to the richness of polyphenols, flavonoids and stilbenes in foods and

beverages may protect against oxidative stress, thereby preventing cellular oxidative reactions and scavenging reactive oxygen species (Tozzi Ciancarelli et al. 2011, Panagiotakos et al. 2004). Accordingly, a beneficial effect on oxidative stress-related diseases has been observed in response to the intake of nuts (Ros et al. 2004), pomegranates (Malik & Mukhtar 2006), tomatoes (World Cancer Research Fund/American Institute for Cancer Research 2007), coffee (Andersen et al. 2006), tea (Cabrera et al. 2006), and red wine (Cordova et al. 2005). Moreover, recent findings suggest that a polyphenol-rich diet is associated with decreased levels of inflammatory biomarkers and an improvement in cardiovascular risk factors such as low density lipoprotein-cholesterol, high density lipoprotein-cholesterol and systolic and diastolic blood pressure (Medina-Remón et al. 2017). In the PREDIMED Study, a long-term multicenter trial, subjects at cardiovascular risk were assigned to a low-fat diet and two different Mediterranean patterns, with olive oil or nuts. Consumption of the MD enriched with olive oil reduced levels of oxidized low density lipoprotein-cholesterol more than the nut-rich MD. Conversely, the latter was more effective in increasing high density lipoproteins and in decreasing triglyceride levels. (Fitó et al. 2007). Therefore, according to the mentioned studies, most of the food components characterizing the MD pattern seem to have functional properties and, as reported by one of the working definitions of functional foods (International Food Information Council 2012) “*may provide a health benefit beyond basic nutrition and may play a role in reducing or minimizing the risk of certain diseases and other health conditions*”. Globally, available findings confirm the apparent positive effect of most of the food components of the MD pattern on a number of functions and parameters such as endothelial function, blood pressure, blood lipid profile and

platelet responsiveness and the related cascade of events (Ortega 2006, Chrysohoou et al. 2004, Martínez-González et al. 2016, Calcabrini et al. 2017, Koloverou et al. 2016, Aparicio-Soto et al. 2016). Over the past few years, studies have suggested that the positive effects of the MD on health status could be ascribed not just or not so much to individual constituents but rather to the synergic and combined interaction between foods and their bioactive components which as a whole are the supporting structure of the MD (Menotti et al. 2012, Sofi et al. 2008, Sofi et al. 2014, Asif et al. 2013, Iriti & Vitalini 2012). Many studies underline that health benefits are associated with strict adherence to the MD and strongly prove that an unhealthy eating habit, such as the intake of highly processed foods (Katz & Meller 2014) represents an insidious risk factor for non-communicable diseases in both the developing and developed world (Caretto & Lagattolla 2015, Alsaffar 2016).

Most dietary patterns which have been studied for their healthy properties (e.g. DASH, Mediterranean or Nordic diets) are based on very similar principles that respect the environment and can be easily achieved at the population level (Katz & Meller 2014, Lacoppidan et al. 2015, Sacks et al. 1999). Particularly, considerable importance was attributed to the use of natural foods which should be prioritized over processed foods and industrially produced trans fats and simple sugars (Niebylski et al. 2015, Leclercq et al. 2009, Sette et al. 2011). Despite that clear recommendations on proper eating behaviour have been consistently emitted by governments and health agencies, the major challenge remains to change the current unhealthy and unsustainable dietary patterns in the general population around the world. Indeed, as recently observed, improving dietary habits of the population has proven extremely difficult, as well as encouraging people to adopt sustainable dietary changes which

limit environmental impacts, beyond the mere nutritional value (Horgan et al. 2016).

### **3. The Mediterranean Diet: current concerns**

There is a general agreement to believe that the health promotion due to a high adherence to MD may be ascribed to its strong influence on decreasing the inflammatory processes and increasing the antioxidant defenses, so counteracting the interactive relationships between inflammation, oxidative stress and related diseases (Mangge et al. 2014, Dai et al. 2008, Psaltopoulou et al. 2013 Reedy et al., 2014). The high content of compounds with antioxidant and anti-inflammatory activity present in most foods of the MD pattern (legumes, dried and fresh fruits, vegetables, fish, extra virgin olive oil) has been considered effective in counteracting cellular degeneration, proliferation of cancer cells, and improving the intestinal function as well as for regulating metabolic parameters (Sofi et al. 2014, Ortega, 2006, Aparicio-Soto et al. 2016, Reedy et al. 2014, Huang & Davidge 2013). The identification and the evaluation of bioactive constituents of the MD are, therefore, crucial to confirm the MD pattern as an effective tool for the maintenance of health status and prevention of chronic diseases and cancer due, at least in part, to an unhealthy eating behaviour and lifestyle. Particular emphasis has been given to the protective effects of polyphenols, common food constituents of plant origin characterized by a variety and complexity of chemical structure responsible for their biological properties and bioavailability (Tapiero et al. 2002, D'Archivio et al. 2007). Several studies have tried to evaluate through which mechanisms polyphenol-rich foods could exert a health benefits and most of the findings underlined that their favourable influence on health status is due to powerful antioxidant activities of the polyphenol content in them (Hernández et al.

2017, Fitò et al. 2007, Aparicio-Soto et al. 2016, Malik & Mukhtar, 2006). Effectively, it has observed that after consumption of polyphenol-rich foods, blood plasma values of Total Antioxidant Capacity (TAC) may increase, shortly or after a little more time depending on polyphenol concentration in foods ingested and if they were beverages or solid foods (Hollman et al. 2011, Pellegrini et al. 2003, Pellegrini et al. 2006). Noteworthy, the effect was transient and blood plasma TAC values return to baseline values after a few hours (Hollman et al. 2011). Recently, some evidence has been provided on the possible differences between acute effects on some surrogate markers for cardiovascular risk following acute consumption of some polyphenol-rich foods and longer-term effects due to their chronic/habitual intake. Recent findings suggest that a chronic response of the vascular endothelium might be distinguished from the acute response and that chronic/regular intake of dietary polyphenols might result as a promising and effective nutritional strategy for health and diseases management (Miranda et al. 2016, Davinelli & Scapagnini 2016). However, the possible mechanisms underlying the observed differences between acute and long-term effect on markers must still be confirmed (Sies 2010, Tozzi Ciancarelli et al. 2011). In the early 1990's, red wine gained great attention to explain the epidemiological observation on the low incidence of cardiovascular disease in French people, despite consuming a diet high on saturated fats ("the French paradox") (Renaud & de Lorgeril, 1992). The Authors suggested that the inhibition of platelet reactivity by wine could have been one explanation for protection from coronary heart disease (CHV) in France people. In the attempt to verify the attractive relationship between antioxidant activity of red wine non-alcoholic components and platelet's responsiveness, a plethora of interesting studies were published, but the results

remain even today discordant and far from being conclusive (De Lange et al. 2003, Goldberg et al. 2003, Gresele et al. 2008, Tsang et al, 2005, Tozzi Ciancarelli et al. 2011). Bioavailability of polyphenols is limited and their concentrations within the systemic circulation and tissues are very low in comparison with endogenous antioxidants, such as uric acid or ascorbic acid (Sies 2010, Hollman et al. 2011, Ciancarelli et al. 2015). Therefore, they could be well below those needed to achieve the biological effects observed *in vitro* experiments or in laboratory animals. Notably, once ingested, the polyphenolic molecules undergo the extensive metabolism that reduces their antioxidant activity and leads to the presence within the circulation of a mixture of compounds whose bioactivity in the systemic circulation must be demonstrated. (Sies 2010, Hollman et al. 2011, Tarascou et al. 2010, Carlsen et al. 2010, Del Rio et al. 2010). Foods which are produced for human nutrition have significant consequences for both the environment and health of a given population (Sáez-Almendros et al. 2013) and, in turn, the environment may handle food choices and affect eating habit (Baroni et al. 2007). Climate changes, toxic emissions and greenhouse gas emissions have caused profound changes in the planet that are reflected on agriculture and food availability. Notably, food intake contributes substantially to our exposure to environmental contaminants. Food choices and agro-food-industry practices as well as trade policies should take due account of environmental footprints.

Heavy metals intake by human populations through the food chain are important environmental pollutants. Their presence in the atmosphere, soil and water, and bioaccumulation in the food chain even in traces could cause deleterious effects for human health (Islam Eu et al. 2007). Moreover, intensive agronomic practices can affect bioavailability and crop accumulation

of heavy metals, thus influencing the thresholds for assessing dietary toxicity of heavy metals in the food chain (Yousaf et al. 2016).

#### 4. Conclusions and prospects

In these last years, evidence is provided on the interesting molecular effects of polyphenol-rich foods beyond their role as antioxidants. Accordingly, it has been shown that flavonoids can modulate the activity of enzymes involved in the metabolism of arachidonic acid and that flavonoids-induced inhibition of these enzymes may decrease the production of prostaglandins, leukotrienes, and peroxynitrate, deleterious mediators of inflammation (Sies 2010, Hollman et al. 2011). Interestingly, *in vitro* experiments suggested that tea polyphenols increase the activity of the enzyme producing nitric oxide in blood vessel endothelium, thus having an important influence on the so called flow-mediated dilation, a physiological vascular response to transient ischemia (Anter et al. 2004). Currently, research looks with great interest to nutritional "omics" technologies for elucidating the possible role of bioactive food components in health promotion. (Kakkoura et al. 2017, Vázquez-Fresno et al. 2015). Measurement of the food metabolome, indeed, could provide important insights into the relations between dietary exposure, food composition, and the risk of major chronic diseases.

The MD is widely considered a sustainable diet model that presents a very low environmental footprint, promotes biodiversity and protects human health and well-being (Alsaffar 2016, De Boer et al. 2007). However, we must not ignore the emerging and serious global aspects that might convert the traditional MD pattern into a theoretical eating model far away from that described by Keys.

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