REVIEW

Implication of the Mediterranean diet on the human epigenome

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Keywords

Epigenetics • Mediterranean Diet • Nutriepigenetics • Polyphenols

Summary

Epigenetics, defined as "hereditary changes in gene expression that occur without any change in the DNA sequence", consists of various epigenetic marks, including DNA methylation, histone modifications, and non-coding RNAs. The epigenome, which has a dynamic structure in response to intracellular and extracellular stimuli, has a key role in the control of gene activity, since it is located at the intersection of cellular information encoded in the genome and molecular/chemical information of extracellular origin. The focus shift of studies to epigenetic reprogramming has led to the formation and progressive importance of a concept called "nutriepigenetics", whose aim is to prevent diseases by intervening on nutrition style. Among the diet types adopted in the world, the renowned Mediterranean Diet (MD), being rich in unsaturated fatty acids and containing high levels of whole grain foods and large quantities of fruits, vegetables, and legumes, has shown numerous advantages in excluding chronic diseases. Additionally, the fact that this diet is rich in polyphenols with high antioxidant and anti-inflammatory properties has an undeniable effect in turning some cellular pathways against the disease. It is also apparent that the effects of polyphenols on the epigenome cause changes in mechanisms such as DNA methylation and histone acetylation/deacetylation, which have a regulatory effect on gene regulation. This review presents the effects of long-term consumption of nutrients from the MD on the epigenome and discusses the benefits of this diet in the treatment and even prevention of chronic diseases.

Introduction

The concept of epigenetics, which was first defined by Conrad Waddington in 1942, was discussed as the gene-environment interaction established between genotype and phenotype in the developmental process [1]. The currently accepted definition of epigenetics, which etymologically means "above gene", is "hereditary changes in gene expression that occur without any change in the DNA sequence". Although the 21st century is defined as the "century of epigenetics", it carries out studies in this field by targeting various epigenetic marks, such as DNA methylation, histone modifications, and non-coding RNAs, in the control of cellular processes. In the genome, which is constituted of all of the genetic information contained in cell DNA, these epigenetic marks have extremely stable and dynamic structures, but they can also lead to changes in the epigenetic state when influenced by environmental factors [2].

On the other hand, the complex modifiers associated with genomic DNA that enable the transfer of unique cellular and developmental identity constitute the epigenome. In other words, the epigenome, which includes any gene expression modifier that is independent from the DNA sequence in said gene, is the chain of chemical tags that can modify the DNA and the structures associated with it. Therefore, the epigenome is at the intersection of the cellular information encoded in the genome and the molecular/chemical information of extracellular origin.

Over the last two decades, once genetic information has become understandable, the focus of studies in this field has shifted to epigenetic reprogramming. In this context, studies about nutrition, which is an indispensable part of human life, have drawn attention to the importance of epigenetic studies, especially those focusing on the mission of preventing diseases. Among the many types of diet, it is frequently discussed within the framework of precision and preventive medicine that the Mediterranean Diet (MD) plays an effective role in reducing the prevalence of many chronic diseases. This review will discuss current approaches to the role of the MD in epigenome control, as personalized medicine and disease prevention strategies are gaining importance today.

An overview of the elements that make up human epigenome

Together with the genome, the epigenome establishes a unique gene expression program to define the functional identity that is unique to each cell type, plus the

https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2746

developmental or disease processes. At the same time, the epigenome plays a role in the development of the organism's ability to respond to some environmental stimuli. Therefore, unlike the stable genome, the epigenome is characterized by a dynamic and variable behavior in response to intra- and extracellular stimuli. Maintaining this dynamic structure and activating gene regulation mechanisms from the developmental process essentially require the formation of epigenetic memory. In the formation of this epigenetic memory, the interactions of the epigenome with the environment affect the activation process of genes. Therefore, it is worthy of consideration that the epigenome of an individual is not only hereditary, but it can also be shaped by exposure to certain environmental factors during the prenatal period [3]we are still far from understanding the molecular events underlying phenotypic variation. Epigenetic modifications to the DNA sequence and associated chromatin are known to regulate gene expression and, as such, are a significant contributor to phenotype. Studies of inbred mice and monozygotic twins show that variation in the epigenotype can be seen even between genetically identical individuals and that this, in some cases at least, is associated with phenotypic differences. Moreover, recent evidence suggests that the epigenome can be influenced by the environment and these changes can last a lifetime. However, we also know that epigenetic states in real-time are in continual flux and, as a result, the epigenome exhibits instability both within and across generations. We still do not understand the rules governing the establishment and maintenance of the epigenotype at any particular locus. The underlying DNA sequence itself and the sequence at unlinked loci (modifier loci.

Epigenetic modifications enable chromatin organization and maintain cellular function by creating inherited transcription conditions. This type of regulation occurs through DNA and histone and chromatin modifications, which occur by packaging histone-binding proteins. The epigenome is shaped differently depending on the cell type, usually involving reversible mechanisms via its epigenetic marks. The mechanisms responsible for this regulation are DNA methylation – the most important element of DNA modifications that have a direct effect on the epigenome – and chromatin modifications, including histone acetylation, histone methylation, histone deimination, glycosylation, ADP ribosylation, histone ubiquitination, histone sumoylation, histone phosphorylation, nitrosylation, biotinylation. Apart from these mechanisms, non-coding RNA-mediated RNAi mechanisms, which have an important role in targeted gene silencing, have been studied frequently in recent years, thus opening a new horizon in studies in the field of epigenetics.

DNA MODIFICATIONS THAT ACT DIRECTLY ON THE EPIGENOME: DNA METHYLATION

Epigenetic marks are an important component of the epigenome because they cause diverse effects on gene expression. Since the transformation into a specific cell type from the very early stages of embryogenesis is considered as a "software" encoded in the epigenome, it can be concluded that the epigenome plays a leading role in defining cell functions [4]. Notwithstanding, within the scope of the measures taken to prevent metabolic syndromes (such as diabetes) in the early stages of life, the fact that dietary styles cause permanent changes in DNA methylation is among the issues that have been frequently emphasized in the recent years. In fact, there is growing evidence that nutrition has an impact on DNA methylation, which is one of the largest and most studied epigenetic mechanisms that play a key role in gene expression maintaining [5].

The core of this mechanism is the conversion of cytosines in regions where CpG islands (sometimes also called "CpG clusters") are dense to 5-methyl cytosines (5mC), undertaking the task of suppressing gene expression by blocking transcription factors [6]. DNA methylation, which plays an important role in gene expression and chromatin organization and is a part of the normal developmental process, largely occurs in the early postnatal period and during development. Recent studies demonstrated a strong link between DNA methylation and human diseases, directing post-genome era studies in this field. In this respect, its effect on nutrigenomics is a separate research topic in itself.

The mechanism of DNA methylation in mammalians is based on DNA methyltransferases (DNMTs), which are responsible for establishing methylation models throughout the genome, and methyl-CpG binding proteins (MBDs), which are responsible for reading the relevant marks. Among the DNA methyltransferases, those classified as DNMT3A and DNMT3B are the two main enzymes responsible for *de novo* methylation, having functions such as methylation remodeling and suppression during embryogenesis. DNMT1, another critically important, plays a role in establishing the methylation pattern and suppressing transcription by specifically targeting hemi-methlyated CpG sequences. Enzymes such as DNMT2 and DNMT3L, which play ancillary roles in the formation of the complex, have also been identified [7, 8]. Deregulations in DNA methylation, being a dynamic mechanism and playing a pivotal role in controlling the timing of cellular processes, have been associated with many diseases such as cancer, cardiovascular diseases, and predisposition to obesity [9].

Chromatin modifications that act directly on the epigenome: Histone modifications

Chromatin is an entire highly condensed DNA-protein complex, whose structural and functional unit is the so-called "nucleosome", that forms the backbone of essential nuclear processes – such as replication, transcription, and DNA repair – in all eukaryotes. It exists in two functional forms, euchromatin and heterochromatin, which are conceptually different from each other. Euchromatin is a highly loosely condensed form that is transcriptionally active and provides the environment for DNA-regulatory processes, while heterochromatin is often defined as its tightly condensed transcriptionally inactive form, devoid of DNA-regulatory activity [10]. Histones are evolutionarily well-conserved proteins.

There are two copies of each of the H2A, H2B, H3, and H4 histones in the octamer nucleosome, and their organization is completed when 147 bp DNA wraps around this octamer structure twice [11].
Histone modifications that develop after the translational process in the transfer and after the processing of epigenetic information include more than 200 modifications, which occur at the amino-terminal ends of the histone proteins. These modifications predominantly include cellular events such as acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation, and have been extensively linked to gene activity, gene silencing, or isolation between active and inactive gene regions– similar to DNA methylation [6]. All these modifications cause a change in the structure of chromatin, neutralizing the electrostatic charge of histone tails, as well as leading to the formation of different histone codes and activating or inactivating transcriptions [6, 12].
It should be noted that histone modifications have always been more striking than DNA methylation, due to the fact that the latter's properties can be reversed by applying certain nutrition styles throughout the life span from the periconceptional period [13]which cause heritable changes in gene expression without changes in DNA sequence. Nutrient-dependent epigenetic variations can significantly affect genome stability, mRNA and protein expression, and metabolic changes, which in turn influence food absorption and the activity of its constituents. Dietary bioactive compounds can affect epigenetic alterations, which are accumulated over time and are shown to be involved in the pathogenesis of age-related diseases such as diabetes, cancer, and cardiovascular disease. Histone acetylation is an epigenetic modification mediated by histone acetyl transferases (HATs. Therefore, the protection of chromatin structure by regional relaxations and rearrangements has a key role in processes like DNA replication, DNA repair, and gene transcription; it also underlies dynamic changes within the epigenome. The fact that the enzymes involved in the process of providing this dynamic structure work in opposition to each other show that such modifications have reversible properties. Although there is coordination in all types of histone modifications in the control of chromatin structure, the process is complicated by the interactions between DNA methylation and ATP-dependent chromatin remodeling elements [14].
Among the most interesting studies conducted to understand the role of nutrition in the regulation of these modifications are histone acetylation and deacetylation, which have been studied for decades in different aspects of omics sciences. In this context, it would be beneficial to briefly give the basic outlines of these mechanisms that play a key role in modulating the epigenome. Histone acetylation is a reversible covalent modification that is observed at specific lysine residues of histone tails, which causes the positive electrical charge of the target lysine to become neutral, thereby weakening the electrical attraction between histone-DNA or nucleosome-nucleosome [14]. The enzymes involved in the process are the Histone Acetyltransferases (HATs), which are able to catalyze the transfer of the acetyl ($O = C\text{-}CH_3$) group to the ε-amino group of the lysine chains at the N-terminus of histone tails, using acetyl CoA as a cofactor. Notably, these enzymes neutralize lysine's positive electrostatic charge, thereby causing relaxation of the attraction between histones and DNA. In contrast to this process, Histone deacetylases (HDACs) are involved in the deacetylation process (that is the recycling process of acetylation); these enzymes remove the $O{=}C\text{-}CH_3$ group in the ε-N-acetyl-lysine amino acid in histone and give the lysine a positive charge again. As a result of this reaction, the histone DNA connection is tightened and the local chromatin structure is closed to transcription in a stable state [15].
The elucidation of the molecular mechanisms underlying the reversibility of histone modifications, apart from showing new ways in the treatment scheme of many diseases, has led to the idea that nutrition styles will have an undeniable effect on shaping these histone modifications, and has also recently increased the interest in studies in this direction.

Non-coding RNA-mediated interactions: RNAi

The concept of RNAi was first introduced in 1998, when Andrew Fire and Craig Mello demonstrated the role of double-stranded RNA (dsRNA) in post-transcriptional gene silencing (PTGS) in *C. elegans*, demonstrating that non-coding RNAs play a central role in the gene expression of multicellular organisms [16]. RNAi has been an important part of research in the development of many treatment strategies in addition to the histone modifications because of its convenience in investigating gene function comprehensively, which also makes it a useful tool in the intervention and modification process in the mammalian genome [17]. This technique was developed as an anti-sense strategy and, since it targets the mRNA inside the cell, it is essential to transfer into the cells a DNA or RNA nucleic acid chain that is reverse complementary to this mRNA. Thus, the mRNA is degraded by catalytically active oligonucleotides, preventing the translation of mRNA. In fact, this mechanism is part of an advanced cellular defense system, developed to protect its genome against foreign pathogens. However, including small molecules – such as small interfering RNAs (siRNAs) and microRNAs (miRNAs) – in these pathways was proven to have important functions in gene regulation, which led to its use in molecular biology studies to suppress endogenous genes [18].
siRNAs are of fundamental importance in the mechanism of RNAi by downregulating target mRNAs through endonucleolytic cleavage. In the setup of the RNAi pathway, dsRNAs are reduced to fragments of 20-22 nucleotides, thereby binding to the complementary part of target mRNAs and degrading them [19]. Although the microRNAs have a similar pathway to siRNAs, they are formed from precursor RNA molecules with a stem-loop secondary structure and play a key role in biological processes such as development, differentiation, cell proliferation, and apoptosis. Dysregulations in miRNAs are associated with many chronic diseases (in particular

cancer) and other epigenetic changes that occur together, changing the chromatin structure and thus also the interaction of proteins that is necessary for transcription with DNA. Although it is not possible to go into details of the molecular mechanism of the RNAi process in this review, whose aim is to discuss the MD, nutrigenomic studies conducted in recent years focus on the effects of diet contents on the epigenome by targeting molecules in this regulatory pathway.

The influence of diet on shaping epigenetic mechanisms

Nutrition, being one of the indispensable elements for survival and healthy life, has become an interesting topic because of its evolution into many different patterns of social behavior created by different populations. The plant- and animal-derived nutrients bestowed on them by nature in the land each people inhabited not only shaped many different cultural cuisines, but also paved the way for the utilization of these nutrients as alternative medical treatments. Although there are differences in cultural bases, the global effect of the age we live in has led to the convergence of nutritional needs by coming together on a common denominator. As the most obvious example of this, the adoption of the Western Diet (WD) by almost all societies has made it the most accessible form among people's daily routine activities. However, it is obvious that this diet, being rich in saturated fatty acids, on the long run can cause disorders in glucose and insulin regulation, thus paving the way for the accumulation of fat in the body and an increased risk of many chronic diseases, such as cancer and metabolic syndromes [20, 21].

The emergence of numerous different diets in modern dietary patterns has led to a selective competition in establishing a dynamic balance between cellular metabolisms depending on the food source. In this context, observational studies and randomized controlled trials have revealed that the Mediterranean Diet (MD), which is rich in unsaturated fatty acids, has many advantages in reducing the risk to develop diseases such as Type-2 Diabetes Mellitus (T2DM), obesity, cardiovascular diseases (CVD), and cancer [22]. The MD is a sustainable diet type that is substantially rich in polyphenols, contains high levels of whole-grain foods, and supports the consumption of plenty of vegetables, fruits, and legumes [23, 24]. Additionally, it supports the intake at moderate levels of basic foods such as poultry, fish, and eggs, with the omega-3 fatty acids it contains; also, the consumption of red wine at meals is accepted as a part of this diet. Unlike the Western Diet, consumption of red meat and processed meat is allowed at a lower level, while confectionery products with low or scarcely any nutritional value are minimal [25].

Prior to associating nutrition with epigenetics, it is noteworthy to emphasize the importance of DNA repair mechanisms that are responsible for the protection of genomic stability against any DNA damage. These mechanisms, which preserve the stability of the genome, primarily detect lesions in DNA and enable mechanisms such as base/nucleotide excision repair mechanisms or non-homologous end-joining (NHEJ) and homologous recombination (HR), based on single-strand breaks (SSBs) or double-strand breaks (DSBs) [25, 26]. These repair mechanisms, which act as a shield against DNA damage, are conspicuously present in neoplastic diseases. Although germline mutations are effective in the formation of genomic instability in caretaker genes, particularly in hereditary cancers, this inactivation in sporadic cancers is characterized by the accumulation of DSBs as a result of collapsed DNA replication forks [27]. In this process, which is called oncogene-induced DNA replication stress model, the fact that the MD, known for its protective effect against cancer, provides the necessary metabolic substrates and strengthens genomic maintenance demonstrates that nutrition plays a dominant role in epigenome [25].

As mentioned above, many in vivo studies have shown that dietary habits not only affect the genomic stability of the organism, but they also have a shaping effect on the epigenome. For this purpose, the differences between high-fat and/or high-sugar diets were examined, revealing that the effects of dietary components on histone acetylation and deacetylation were more favorable to living a healthy life when the subjects followed calorie-restricted diets [13]. To illustrate this phenomenon with a few examples, the offspring of Japanese macaques that followed a high-fat diet during pregnancy had higher histone H3 acetylation levels, while the opposite was observed in the offspring of mothers fed a lower-fat diet [28]. Similarly, rats on a high-fat diet showed a significant decrease in liver regeneration abilities, suggesting that this may be consistent with a significant decrease in HDAC activities [29]. All these findings together show that high-fat and/or high-sugar diets can lead to metabolic syndromes by negatively affecting liver functions.

The tight link between nutrition and epigenetics from past to present: The Dutch Famine

Epidemiological studies carried out so far have underlined that the dietary style adopted in childhood and adolescence causes several alterations in gene expression levels; those epigenetic factors play an important role in this regard [30]. In fact, this knowledge became even more significant with the evaluation of metabolic parameters, strikingly revealing that the individual is not only dependent on his/her own diet, but also influenced by his/her parents' diet [5, 31]. It is undeniable that all the factors that the mother is exposed to during pregnancy might lead to epigenetic changes and, accordingly, the predisposition of the fetus to possible diseases that may develop throughout his/her life can be shaped at different levels [32-35].

For example, the famine suffered by the population of the Netherlands during World War II (September 1944-May 1945, known as the "Dutch Hunger Winter") that

Tab. I. Classification of polyphenol groups according to the dietary sources in the Mediterranean Diet and their effects on the cellular processes and epigenome they are involved in.

Subclasses of polyphenols	Phenolic compounds	Bioactive Compounds	Dietary sources in MD		Biological activity	Cellular processes involved	Epigenetic mechanism(s)	Reference(s)
Phenolic Acids	Hydroxybenzoic acids	p-hydroxybenzoic acid (pHBA), 3,4-dihydroxybenzoic acid (DHB; protocatechuic acid), 3,4,5-trihydroxybenzoic acid (Gallic acid), Vanillic acid	Red fruits, black radish, pomegranate, onions, berries, nuts		• Anti-oxidant and anti-inflammatory activities • Anti-tumorigenic and neuroprotective effects	• Cell cycle arrest, and induction of apoptosis • Promoting autophagy and inhibition of oxidative stress in neurons	Inactivation of HATs, activation of HDACs	[54, 78]
	Hydroxycinnamic acids	Cinnamic acid, p-Coumaric acid, Ferulic acid, Caffeic acid, Chlorgenic acid, Rosmarinic acid, Sinapic acid	Blueberries, kiwis, plums, cherries, coffee		Anti-oxidant and anti-inflammatory activities	Regulating autophagy and protective effect against DNA damage, cell cycle arrest, and apoptosis induction	Inhibiting HDACs and DNMTs	[60, 79]
Flavonoids	Flavonols	Quercetin, Kaempferol, Myricetin	Onions, broccoli, blueberries, apples, peppers, tomatoes		Free radical scavenging activity together with its anti-oxidant and anti-inflammatory properties	Inhibition of cell proliferation and tumor growth, induction of apoptosis	Influencing effects in miRNA expression patterns related to inflammation	[60, 80]
	Flavanones	Naringenin, Hesperetin, Eriodictyol	Citrus fruits (such as grapefruit, lemons, oranges, etc.)		Anti-oxidant and anti-inflammatory activities	Protection of pancreatic β cells in late stages of diabetes	Inhibitory effect on histone acetylation and decreased histone methyltransferase activity	[81]
	Isoflavones	Genistein, Daidzein, Glycitein	Legumes, soybeans, red clovers		Chemopreventive effects due to its anti-oxidant and anti-inflammatory effects	Inhibition of cell proliferation and tumor growth, induction of apoptosis	Dose-dependent epigenetic roles in DNMT inhibition and histone acetylation	[60, 82]
	Flavones	Apigenin, Luteolin	Cereals, parsley, artichokes, cabbages		Chemopreventive effects due to its anti-oxidant and anti-inflammatory effects	Inhibition of DNA replication, stimulation of apoptosis	Inhibition of DNMTs and HDACs activity	[60, 82]
	Flavanols	Catechins, Epigallocatechin-3-gallate (EGCG)	Green tea, cocoa, berries, nuts		Anti-oxidant and anti-angiogenic activity	Inhibition of cell proliferation and tumor growth, induction of apoptosis, protection against oxidative stress	Inactivation of DNMTs and HATs, activation of HDACs	[13, 48, 54]
	Anthocyanins	Cyanidin, Malvidin, Delphinidin, Pelargonidin, Peonidin, Petunidin	Berries, pears, apples, red cabbage, black soybean, grapes, blackcurrant, peaches		Anti-oxidant, anti-inflammatory, anti-mutagenic and anti-adipogenic effects	• Cell growth inhibition, cell cycle arrest and induced apoptosis • Decrease in inflammatory cytokines such as CRP and TNF-α	Alterations in H3K4me3 levels and DNMTs activities	[60, 83-85]
Other polyphenols and their bioactive compounds		**Dietary sources in MD**	**Biological activity**		**Cellular processes involved**	**Epigenetic mechanism(s)**	**Reference(s)**	
Stilbenes	Resveratrol, Pterostilbene, Pallidol	Red wine, grapes, blackberry, blueberry, mulberry, peanuts, etc.	Cardioprotective, neuroprotective, and chemopreventive effects		• Promoting apoptosis, inhibition of cell proliferation. • Regulating signaling pathways involved in meiosis, inhibitory effect on angiogenesis, inhibition of NF-κB activation	Inhibition of DNMTs and HDACs, leading to activation of HATs	[48, 51, 60]	
Lignans	Secoisolariciresinol, Matairesinol, Arctigenin, Nordihydroguaiaretic acid (NDGA), Pinoresinol	Extra-virgin olive oil (EVOO), tea, coffee, whole grains	Chemopreventive effects due to their anti-oxidant and anti-inflammatory effects		Cell cycle arrest and apoptotic activity	Induction of DNA demethylation and upregulation of H3K9me3	[86, 87]	
Curcuminoids	Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin	Turmeric, ginger, curry powder	• Anti-oxidant, anti-inflammatory, anti-microbial effects. • Cardioprotective effects		• Inhibition of cell proliferation and tumor growth, induction of apoptosis • Ameliorates the dysregulations in the related pathway of neurodegenerative diseases	• Induced histone hypoacetylation and decreased DNMTs activity. • Decrease in HDAC1 expression levels by inhibiting matrix metalloproteinase-2 (MMP-2)	[48, 53, 60, 88, 89]	
Organosulfur compounds	Sulforaphane, Isothiocyanates	Cruciferous vegetables (broccoli, cabbage, kale, cauliflower, Brussel sprouts, etc.)	• Chemopreventive effects due to its anti-tumoral properties • Increased antioxidant and anti-inflammatory capacity in neurodegenerative diseases		• Cell cycle arrest and induction of apoptosis • Promoting autophagy and inhibition of oxidative stress in neurons	• Inhibition of HDAC activity, increased histone acetylation levels • Decreased DNA methylation levels in nuclear factor erythroid 2-related factor 2 (Nrf2) promoter	[90-95]	
Tyrosols	Hydroxytyrosol, Oleuropein, Ligstroside	Olive leaf, extra-virgin olive oil (EVOO)	• Antioxidant, anti-inflammatory, and antiatherogenic effects • Anti-viral properties		• Inhibition of proliferation in cancer cell lines by preventing DNA damage • Inhibition of viral replication by causing down-regulation of endocytosis-related genes	• Modulation of distinct miRNA expression levels • Inhibition of several HDACs	[24, 76, 77, 96, 97]	

caused the death of approximately 20,000 people, led to an understanding of the importance of fetus' nutrition during pregnancy and even in the period before conception [35-37]. According to available reports, children born to women who became pregnant during the famine were found to be more prone to diabetes, cardiovascular diseases, various kinds of cancer, and a number of mental problems later in life [36, 38, 39].

Considering the pregnancy periods separately, it was observed that the birth weight of babies born to women who suffered from the famine during the first trimester was not affected, but there was an increased risk of obesity and CVDs as compared to those who were exposed to starvation in adulthood [40]. As the strongest evidence of this situation on DNA methylation, it can be acknowledged that changing methylation levels in Insulin Receptor (*INSR*) and Carnitine Palmitoyltransferase 1A (*CPT1A*) genes shapes the susceptibility to related diseases, which play important roles in prenatal growth and fatty acid oxidation, correspondingly [41]. However, it has been observed that the children of women who were exposed to famine in the third trimester, which is among the later stages of pregnancy, presented a lower birth weight, while the incidence of hypertension increased, together with a significant increase in insulin resistance [42]. Although changes in the DNA methylation process are observed to play an important role in determining disease predispositions, insulin-like growth factor II (*IGF2*), which is known to have important functions in the developmental process and is one of the best characterized epigenetically-regulated loci, draws attention. Maternally imprinted *IGF2* is provided by the differentially methylated region (DMR), and *IGF2* DMR methylation is determined by various genetic factors, providing the preservation of the methylation mark until middle age [43, 44]. In fact, a study conducted by Heijman et al. has led to the observation that the methylation level of *IGF2* DMR is lower in babies born years later, when mothers are deprived of essential amino acids such as methionine (the methyl donor) during the periconceptional process. However, considering the results of the same study, it was found that the children of women who were exposed to famine later in pregnancy were born with lower birth weight, but there was no change in *IGF2* DMR methylation levels [35].

Mechanisms of the Mediterranean diet and its components in achieving epigenetic control on some diseases

Along with extreme factors (such as famine) that people may be exposed to throughout their lifetime, adopting unhealthy lifestyle habits such as a physically sedentary lifestyle, smoking, excessive alcohol consumption, and consuming too much fast foods show that individuals are at higher risk in terms of metabolic diseases, which are the gateway to many chronic diseases. Based on this information, researchers are focusing on the effects that the MD and its contents have on the human epigenome, which might be described as an unopened magic box. It is extremely interesting the fact that diet plays a decisive role in the epigenome maintenance and that the polyphenols contained in the main typical foods of the MD can shape DNA methylation and histone modifications. Although these studies are still scarce, it is possible to discuss in detail how these mechanisms are reflected in literature.

Polyphenols are bioactive molecules that are naturally contained in large quantities in fruit and vegetables and that are responsible for different biological functions: they are thus classified into different groups, such as phenolic acids, flavonoids, and anthocyanins [45]. Phenolic acids are then divided in two subgroups, hydroxybenzoic acids and hydroxycinnamic acids, while flavonoids are divided in many different subgroups, including flavonols, flavanones, flavones, isoflavones, flavanols, and anthocyanins [46]. In addition to flavonoids and phenolic acids, there are also separate groups of polyphenols defined as "secondary plant metabolites", including stilbenes, lignans, and sulforaphanes, which have strong anti-inflammatory and antioxidant effects in the cell and act as a shield against DNA damage [47]. In recent years, researchers have been focusing on studying the effects of these polyphenols, which are largely contained in the foods that make up the MD (being a fruit- and vegetable-based diet) on the epigenome. The biological properties of the polyphenol groups and their components mentioned here, as well as the effects they have on the cellular processes and epigenome they are involved in, are summarized in Table I.

The fact that polyphenols, thanks to their high antioxidant and anti-inflammatory properties, affect in different ways the regulation of epigenetic processes and metabolic activities shows that the MD is more than a diet [48]. Given the fact that diet and lifestyle habits (regular sports activity, healthy sleep, etc.) usually match, many studies reported that a diet rich in monounsaturated fatty acids (MUFAs) positively improves cardiovascular health [49, 50]. For example, cocoa flavonoids have an antihypertensive effect, lowering blood pressure by down-regulating functional genes such as *DNMTs* and *MTHFR*, which are involved in the epigenetic process of peripheral blood mononuclear cells [13, 51, 52]. Animal experimental studies on hypertension have shown that curcumin, which is included in curcuminoids, causes a significant decrease in HDAC1 expression levels by inhibiting the inflammatory marker matrix metalloproteinase-2 (MMP-2) and also causes an evident increase in Tissue Inhibitor of Metalloproteinases 1 (TIMP1) via Histone H3 acetylation [53]. Likewise, the flavanol Epigallocatechin gallate (EGCG), found in green tea, acts as an interesting HAT inhibitor [13, 48], which in among the treatment targets of cardiovascular diseases: inhibiting HAT activation leads to suppressing the activity of Nuclear Factor-kappa B (NF-κB), which is the main member of the inflammation pathway. Keeping all these mechanisms and their interactions into consideration, it is clear to see that the nutrition style of the MD has a

unique role in managing the epigenetic signature on preventing CVDs.

In addition to their cardioprotective effect, polyphenols also play an important role in protecting cognitive activity [54]. Recently, the neuroprotective effects of fish, hazelnut, and olive oil – all ingredients vastly used in the MD – and of their micronutrients, like omega-3 polyunsaturated fatty acids (ω-3 PUFAs), are resonating in the field of nutrigenomics. The ω-3 PUFAs found in fish oil help prevent age-related cognitive loss by affecting DNA methylation in different cells [55]. Resveratrol, which is found in red wine (moderately consumed with meals in traditional MD) and in fruits such as grapes, strawberries, and apples, plays a role in decreasing the risk of Alzheimer's Disease by inhibiting DNMTs and HDACs activities, which lead to the activation of HATs, via chromosome segregation [55-57]. In addition, animal experiments have shown that supplementation of S-adenosyl methionine (SAM), a methyl donor, can alleviate disease-related symptoms by recovering the methylation potential of the *PSEN1* gene [58, 59]. This structure of resveratrol, which significantly affects histone modifications, suggested that it may also have an active role in cell cycle and tumorigenesis processes [60]. In this regard, there are studies demonstrating that resveratrol, which is thought to be a key molecule in maintaining the epigenomic profile, is highly effective in inhibiting proliferation in breast cancer cells by suppressing the Enhancer of Zeste 2 Polycomb Repressive Complex 2 (EZH2), a lysine methyltransferase. The suppression of ERK1/2 phosphorylation is also the basis of the antiproliferative effect created by resveratrol, which has a synergistic effect with the suppression of EZH2 [61]. These effects were not only limited to histone modifications, but also demonstrated a potential therapeutic effect in neuroblastoma by causing the suppression of EZH2 by upregulation of various tumor suppressor microRNAs, like miR-137 [62].

In addition to all its anti-tumorigenic effects, resveratrol also has effects on obesity, which is one of the metabolic diseases caused by the Western Diet. Given the fact that nutritional styles the fetus/baby is exposed to throughout pregnancy and lactation are vigorously linked to the onset of adult diseases, and it has been hypothesized that obesity can be modulated by epigenetic memory in the offspring [63]. In this context, numerous studies have shown that polyphenols in the MD indirectly cause suppression of genes that regulate adipocyte differentiation and triglyceride accumulation through chromatin remodeling and various histone modifications. Furthermore, mice that were fed a high-fat diet showed increased DNA methylation in the *Leptin* and *Pparg2* gene promoters and proinflammatory mechanisms were entirely affected [64, 65]. To reinforce the effect of polyphenols on adipokinesis with an example, quercetin, a flavonol found in onions and kale, and resveratrol, a prominent stilbene, are observed to cause a significant decrease in the levels of CCAAT Enhancer Binding Protein (C/EBPα) and Peroxisome Proliferator-Activated Receptor (PPARγ), which are pro-adipogenic genes, and to negatively regulate adipokinesis [66-68]. Epigallocatechin gallate (EGCG), another type of polyphenol included in the flavanol subclass, which is prominently found in green tea, has long been shown to pave the way for lipolysis by suppressing lipogenesis with pre-adipocyte differentiation and providing beta-oxidation to fatty acids [69, 70]. In cancer, where EGCG is also a potential epigenetic modifying agent, it has gained more attention, as it has been shown to inhibit cell proliferation by binding to enzymatic substrates of DNMT3b and HDAC1 [71, 72]. Moreover, among chromosomal abnormalities, EGCG has been reported to also have a modulating effect at the epigenome level on imbalances in DNA methylation that occur due to the overdose of genes on the 21st chromosome in Down Syndrome [73].

Extra-virgin olive oil (EVOO), one of the most intriguing components of the MD, has a protective effect against many chronic diseases as it is rich in various flavonoids and phenolic acids, as well as other polyphenols such as Oleuropein (OL) and Hydroxytyrosol (HT). HT is among the important phenolic fractions that mainly compose olive oil, and it has many pleiotropic effects that enable it to influence biological functions thanks to its antioxidant, anti-inflammatory, and antiatherogenic effects [24]. In addition, recent studies carried out to investigate its protective effects against SARS-CoV-2 infection have shown that HT extracted from olive leaves effectively reduces viral replication by causing down-regulation of endocytosis-related genes [74, 75]. It was demonstrated that in cancer HT and other secoiridoid glycosides inhibit proliferation in certain cell lines by preventing DNA damage, supporting the idea to employ HT dose-dependent supplementation together with conventional treatments [76, 77]. However, it should be noted that when these olive oil-derived bioactive components are evaluated holistically around omics data, their synergetic effect on disease models might be taken more comprehensively in the near future.

Conclusion and future perspectives

The MD, as the name suggests, has been traditionally adopted by the populations living in the countries with a coast to the Mediterranean Sea, and it is proven that the polyphenolic compounds it contains (thanks to the many fruits and vegetables that make it up) play important roles in preventing many chronic diseases, thanks to their antioxidant and anti-inflammatory properties. Polyphenols are diet-derived natural compounds and, given their numerous beneficial effects on chronic disorders, they can be used as adjuvants in personalized and preventive medicine thanks to their effects on the individual's epigenome. Epigenetics, which is defined as heritable changes in gene expression without any change in the DNA sequence, leads to the shaping of the epigenome with chemical modifications that are caused by environmental factors. Nutrition styles and their effects on human health have attracted the attention of researchers working in the field of nutrition for many years, and

combining the findings obtained from observations with genetic research has led to the formation of the multidisciplinary science known as nutrigenomics. Numerous studies show that epigenome formation is related not only to the later stages of life, but also to the prenatal period, for example to the diet followed by the mother during pregnancy and even to the environment she was exposed before conception, thus leading to disease predispositions that the fetus may develop throughout his/her entire life. The fact that children born to women who were pregnant during the Dutch Hunger Winter, one of the most dramatic events engraved in human history, are more prone to many chronic diseases is the strongest reflection of the transfer of changes created on the epigenome to future generations.

Recently, there is a growing interest in addressing the effects of nutrition on the epigenome in the pathways of inflammation and metabolism. Within this framework, PUFAs such as ω-3 and ω-6, which together with polyphenols are among the main components of the MD, act as transcription factor ligands and play an active role in inflammation-related pathways; also, they are among the strongest evidence that they are a major metabolic regulator in related processes. Similarly, many studies have emphasized the effect of nutrition supplemented with folate- and B-vitamins-rich foods, like broccoli and Brussels sprouts, on the modulation of metabolic processes such as nucleotide synthesis and DNA repair, as well as its shaping effect on DNA methylation and histone modifications.

Considering the data presented in the literature so far, it is revealed that long-term consumption of the nutritional elements of the MD, rich in fruits and vegetables and in polyphenols, is of undeniable importance in the treatment and even in the prevention of many diseases by shaping the epigenome in different directions. It is foreseeable that in the future nutriepigenetics – already attracting a great amount of attention thanks to its role in maintaining a long and healthy life – will be supported by more in vitro and in vivo studies, thus providing new data to the literature, further clarifying its mechanisms, and emphasizing the importance of personalized medicine.

Acknowledgements

None.

Conflicts of interest statement

The authors declare no conflict of interest.

Author's contributions

MD, MB, and TB developed the study design and conceptualization of the research methodology. SK and NG contributed to the manuscript's writing. MD, HA, and MCE contributed to manuscript reviewing and editing processes. All authors have read and approved the final manuscript.

References

[1] Waddington CH. The epigenotype. 1942. Int J Epidemiol 2012;41:10-3. https://doi.org/10.1093/ije/dyr184

[2] Peaston AE, Whitelaw E. Epigenetics and phenotypic variation in mammals. Mamm Genome 2006;17:365-74. https://doi.org/10.1007/s00335-005-0180-2

[3] Whitelaw NC, Whitelaw E. How lifetimes shape epigenotype within and across generations. Hum Mol Genet 2006;15(Suppl 2):131-7. https://doi.org/10.1093/hmg/ddl200

[4] Thiagalingam S. Epigenetic memory in development and disease: Unraveling the mechanism. Biochim Biophys Acta - Rev Cancer 2020;1873:188349. https://doi.org/10.1016/j.bbcan.2020.188349

[5] Kaelin WG, McKnight SL. Influence of metabolism on epigenetics and disease. Cell 2013;153:56-69. https://doi.org/10.1016/j.cell.2013.03.004

[6] Feinberg AP. The Key Role of Epigenetics in Human Disease Prevention and Mitigation. N Engl J Med 2018;378:1323-34. https://doi.org/10.1056/nejmra1402513

[7] Bachman KE, Rountree MR, Baylin SB. Dnmt3a and Dnmt3b Are Transcriptional Repressors That Exhibit Unique Localization Properties to Heterochromatin. J Biol Chem 2001;276:32282-7. https://doi.org/10.1074/jbc.M104661200

[8] Robertson KD. DNA methylation and human disease. Nat Rev Genet 2005;6:597-610. https://doi.org/10.1038/nrg1655

[9] Gupta R, Nagarajan A, Wajapeyee N. Advances in genome-wide DNA methylation analysis. Biotechniques 2010;49(4). https://doi.org/10.2144/000113493

[10] Tamaru H. Confining euchromatin/heterochromatin territory: Jumonji crosses the line. Genes Dev 2010;24:1465-78. https://doi.org/10.1101/gad.1941010

[11] Ramaswamy A, Ioshikhes I. Dynamics of modeled oligonucleosomes and the role of histone variant proteins in nucleosome organization, 1st ed. Elsevier Inc. 2013. https://doi.org/10.1016/B978-0-12-410523-2.00004-3

[12] Prakash K, Fournier D. Evidence for the implication of the histone code in building the genome structure. BioSystems 2018;164:49-59. https://doi.org/10.1016/j.biosystems.2017.11.005

[13] Vahid F, Zand H, Nosrat-Mirshekarlou E, Najafi R, Hekmatdoost A. The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: A review. Gene 2015;562:8-15. https://doi.org/10.1016/j.gene.2015.02.045

[14] Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Res 2011;21(3):381-95. https://doi.org/10.1038/cr.2011.22

[15] Xhemalce B, Dawson MA, Bannister AJ. Histone Modifications. In: Encyclopedia of Molecular Cell Biology and Molecular Medicine, 2011. https://doi.org/10.1002/3527600906.mcb.201100004

[16] Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature 1998;391:806-11. https://doi.org/10.1038/35888

[17] Moffat J, Sabatini DM. Building mammalian signalling pathways with RNAi screens. Nat Rev Mol Cell Biol 2006;7:177-87. https://doi.org/10.1038/nrm1860

[18] Thakur A. RNA interference revolution. Electron J Biotechnol 2003;6:36-46. https://doi.org/10.2225/vol6-issue1-fulltext-1

[19] Katoch R, Thakur N. RNA interference: A promising technique for the improvement of traditional crops. Int J Food Sci Nutr 2013;64:248-59. https://doi.org/10.3109/09637486.2012.713918

[20] Grosso G, Bella F, Godos J, Sciacca S, Del Rio D, Ray S, Galvano F, Giovannucci EL. Possible role of diet in cancer: Systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. Nutr Rev 2017;75:405-19. https://doi.org/10.1093/nutrit/nux012

[21] Castelló A, Amiano P, Fernández de Larrea N, Martín V, Alonso MH, Castaño-Vinyals G, Pérez-Gómez B, Olmedo-Requena R, Guevara M, Fernandez-Tardon G, Dierssen-Sotos T, Llorens-Ivorra C, Huerta JM, Capelo R, Fernández-Villa T, Díez-Villanueva A, Urtiaga C, Castilla J, Jiménez-Moleón JJ, Moreno V, Dávila-Batista V, Kogevinas M, Aragonés N, Pollán M. Low adherence to the western and high adherence to the mediterranean dietary patterns could prevent colorectal cancer. Eur J Nutr 2019;58:1495-505. https://doi.org/10.1007/s00394-018-1674-5

[22] Tripp ML, Dahlberg CJ, Eliason S, Lamb JJ, Ou JJ, Gao W, Bhandari J, Graham D, Dudleenamjil E, Babish JG. A Low-Glycemic, Mediterranean Diet and Lifestyle Modification Program with Targeted Nutraceuticals Reduces Body Weight, Improves Cardiometabolic Variables and Longevity Biomarkers in Overweight Subjects: A 13-Week Observational Trial. J Med Food 2019;22:479-89. https://doi.org/10.1089/jmf.2018.0063

[23] Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr 1995;61:1402S-1406S. https://doi.org/10.1093/ajcn/61.6.1402S

[24] Farràs M, Almanza-Aguilera E, Hernáez Á, Agustí N, Julve J, Fitó M, Castañer O. Beneficial effects of olive oil and Mediterranean diet on cancer physio-pathology and incidence. Semin Cancer Biol 2021;73:178-95. https://doi.org/10.1016/j.semcancer.2020.11.011

[25] de Polo A, Labbé DP. Diet-dependent metabolic regulation of DNA double-strand break repair in cancer: More choices on the menu. Cancer Prev Res 2021;14:403-14. https://doi.org/10.1158/1940-6207.CAPR-20-0470

[26] Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability an evolving hallmark of cancer. Nat Rev Mol Cell Biol 2010;11:220-8. https://doi.org/10.1038/nrm2858

[27] Halazonetis TD, Gorgoulis VG, Bartek J. An Oncogene-Induced DNA Damage Model for Cancer Development. Science 2008;319:1352-5. https://doi.org/10.1126/science.1140735

[28] Aagaard-Tillery KM, Grove K, Bishop J, Ke X, Fu Q, McKnight R, Lane RH. Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. J Mol Endocrinol 2008;41:91-102. https://doi.org/10.1677/JME-08-0025

[29] Tanoue S, Uto H, Kumamoto R, Arima S, Hashimoto S, Nasu Y, Takami Y, Moriuchi A, Sakiyama T, Oketani M, Ido A, Tsubouchi H. Liver regeneration after partial hepatectomy in rat is more impaired in a steatotic liver induced by dietary fructose compared to dietary fat. Biochem Biophys Res Commun 2011;407:163-8. https://doi.org/10.1016/j.bbrc.2011.02.131

[30] Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev 2014;72:267-84. https://doi.org/10.1111/nure.12102

[31] Dominguez-Salas P, Cox SE, Prentice AM, Hennig BJ, Moore SE. Maternal nutritional status, C 1 metabolism and offspring DNA methylation: A review of current evidence in human subjects. Proc Nutr Soc 2012;71:154-65. https://doi.org/10.1017/S0029665111003338

[32] Bryce J, Coitinho D, Darnton-Hill I, Pelletier D, Pinstrup-Andersen P. Maternal and child undernutrition: effective action at national level. Lancet 2008;371:510-26. https://doi.org/10.1016/S0140-6736(07)61694-8

[33] Roseboom TJ, Painter RC, Van Abeelen AFM, Veenendaal MVE, De Rooij SR. Hungry in the womb: What are the consequences? Lessons from the Dutch famine. Maturitas 2011;70:141-5. https://doi.org/10.1016/j.maturitas.2011.06.017

[34] Ruemmele FM, Garnier-Lenglin H. Why are genetics important for nutrition? Lessons from epigenetic research. Ann Nutr Metab 2012;60(Suppl 3):38-43. https://doi.org/10.1159/000337363

[35] Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci USA 2008;105:17046-9. https://doi.org/10.1073/pnas.0806560105

[36] Fransen HP, Peeters PHM, Beulens JWJ, Boer JMA, De Wit GA, Onland-Moret NC, Van Der Schouw YT, Buenode-Mesquita HB, Hoekstra J, Elias SG, May AM. Exposure to famine at a young age and unhealthy lifestyle behavior later in life. PLoS One 2016;11:1-11. https://doi.org/10.1371/journal.pone.0156609

[37] Lumey LH, Stein AD, Kahn HS, Van der Pal-de Bruin KM, Blauw GJ, Zybert PA, Susser ES. Cohort profile: The Dutch Hunger Winter families study. Int J Epidemiol 2007;36:1196-204. https://doi.org/10.1093/ije/dym126

[38] van Abeelen AFM, Elias SG, Bossuyt PMM, Grobbee DE, van der Schouw YT, Roseboom TJ, Uiterwaal CSPM. Famine Exposure in the Young and the Risk of Type 2 Diabetes in Adulthood. Diabetes 2012;61:2255-60. https://doi.org/10.2337/db11-1559

[39] van Abeelen AFM, Elias SG, Bossuyt PMM, Grobbee DE, van der Schouw YT, Roseboom TJ, Uiterwaal CSPM. Cardiovascular consequences of famine in the young. Eur Heart J 2012;33:538-45. https://doi.org/10.1093/eurheartj/ehr228

[40] Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the Dutch famine and disease in later life: An overview. Reprod Toxicol 2005;20:345-52. https://doi.org/10.1016/j.reprotox.2005.04.005

[41] Tobi EW, Goeman JJ, Monajemi R, Gu H, Putter H, Zhang Y, Slieker RC, Stok AP, Thijssen PE, Müller F, van Zwet EW, Bock C, Meissner A, Lumey LH, Eline Slagboom P, Heijmans BT. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nat Commun 2014;5:5592. https://doi.org/10.1038/ncomms6592

[42] Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. Early Hum Dev 2006;82:485-91. https://doi.org/10.1016/j.earlhumdev.2006.07.001

[43] Smith FM, Garfield AS, Ward A. Regulation of growth and metabolism by imprinted genes. Cytogenet Genome Res 2006;113:279-91. https://doi.org/10.1159/000090843

[44] Cui H, Cruz-Correa M, Giardiello FM, Hutcheon DF, Kafonek DR, Brandenburg S, Wu Y, He X, Powe NR, Feinberg AP. Loss of IGF2 imprinting: a potential marker of colorectal cancer risk. Science 2003;299:1753-5. https://doi.org/10.1126/science.1080902

[45] Abbas M, Saeed F, Anjum FM, Afzaal M, Tufail T, Bashir MS, Ishtiaq A, Hussain S, Suleria HAR. Natural polyphenols: An overview. Int J Food Prop 2017;20:1689-99. https://doi.org/10.1080/10942912.2016.1220393

[46] El Gharras H. Polyphenols: Food sources, properties and applications - A review. Int J Food Sci Technol 2009;44:2512-8. https://doi.org/10.1111/j.1365-2621.2009.02077.x

[47] Ganesan K, Xu B. A critical review on polyphenols and health benefits of black soybeans. Nutrients 2017;9:1-17. https://doi.org/10.3390/nu9050455

[48] Kalea AZ, Drosatos K, Buxton JL. Nutriepigenetics and cardiovascular disease. Curr Opin Clin Nutr Metab Care 2018;21:252-9. https://doi.org/10.1097/MCO.0000000000000477

[49] Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr 2005;81:215S-217S. https://doi.org/10.1093/ajcn/81.1.215S

[50] D'Archivio M, Filesi C, Di Benedetto R, Gargiulo R, Giovannini C, Masella R. Polyphenols, dietary sources and bioavailability. Ann Ist Super Sanita 2007;43:348-61.

[51] Valdés L, Cuervo A, Salazar N, Ruas-Madiedo P, Gueimonde M, González S. The relationship between phenolic compounds from diet and microbiota: Impact on human health. Food Funct 2015;6:2424-39. https://doi.org/10.1039/c5fo00322a

[52] Desch S, Schmidt J, Kobler D, Sonnabend M, Eitel I, Sareban M, Rahimi K, Schuler G, Thiele H. Effect of Cocoa Products on Blood Pressure: Systematic Review and Meta-Analysis. Am J Hypertens 2010;23:97-103. https://doi.org/10.1038/ajh.2009.213

[53] Hu J, Shen T, Xie J, Wang S, He Y, Zhu F. Curcumin modulates covalent histone modification and TIMP1 gene activation to protect against vascular injury in a hypertension rat model. Exp Ther Med 2017;14:5896-902. https://doi.org/10.3892/etm.2017.5318

[54] Milošević M, Arsić A, Cvetković Z, Vučić V. Memorable Food: Fighting Age-Related Neurodegeneration by Precision Nutrition. Front Nutr 2021;81-13. https://doi.org/10.3389/fnut.2021.688086

[55] Román GC, Jackson RE, Gadhia R, Román AN, Reis J. Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. Rev Neurol (Paris) 2019;175:724-41. https://doi.org/10.1016/j.neurol.2019.08.005

[56] Lee JH, Wendorff TJ, Berger JM. Resveratrol: A novel type of topoisomerase II inhibitor. J Biol Chem 2017;292:21011-22. https://doi.org/10.1074/jbc.M117.810580

[57] Izquierdo-Torres E, Hernández-Oliveras A, Meneses-Morales I, Rodríguez G, Fuentes-García G, Zarain-Herzberg Á. Resveratrol up-regulates ATP2A3 gene expression in breast cancer cell lines through epigenetic mechanisms. Int J Biochem Cell Biol 2019;113:37-47. https://doi.org/10.1016/j.biocel.2019.05.020

[58] Fuso A, Nicolia V, Cavallaro RA, Scarpa S. DNA methylase and demethylase activities are modulated by one-carbon metabolism in Alzheimer's disease models. J Nutr Biochem 2011;22:242-51. https://doi.org/10.1016/j.jnutbio.2010.01.010

[59] Fuso A, Nicolia V, Pasqualato A, Fiorenza MT, Cavallaro RA, Scarpa S. Changes in Presenilin 1 gene methylation pattern in diet-induced B vitamin deficiency. Neurobiol Aging 2011;32:187-99. https://doi.org/10.1016/j.neurobiolaging.2009.02.013

[60] Carlos-Reyes Á, López-González JS, Meneses-Flores M, Gallardo-Rincón D, Ruíz-García E, Marchat LA, Astudillo-De La Vega H, Hernández De La Cruz ON, López-Camarillo C. Dietary compounds as epigenetic modulating agents in cancer. Front Genet 2019;10:1-14. https://doi.org/10.3389/fgene.2019.00079

[61] Hu C, Liu Y, Teng M, Jiao K, Zhen J, Wu M, Li Z. Resveratrol inhibits the proliferation of estrogen receptor-positive breast cancer cells by suppressing EZH2 through the modulation of ERK1/2 signaling. Cell Biol Toxicol 2019;35:445-56. https://doi.org/10.1007/s10565-019-09471-x

[62] Ren X, Bai X, Zhang X, Li Z, Tang L, Zhao X, Li Z, Ren Y, Wei S, Wang Q, Liu C, Ji J. Quantitative Nuclear Proteomics Identifies that miR-137-mediated EZH2 Reduction Regulates Resveratrol-induced Apoptosis of Neuroblastoma Cells*. Mol Cell Proteomics 2015;14:316-28. https://doi.org/10.1074/mcp.M114.041905

[63] Ma X, Kang S. Functional implications of DNA methylation in adipose biology. Diabetes 2019;68:871-8. https://doi.org/10.2337/dbi18-0057

[64] Zwamborn RAJ, Slieker RC, Mulder PCA, Zoetemelk I, Verschuren L, Suchiman HED, Toet KH, Droog S, Slagboom PE, Kooistra T, Kleemann R, Heijmans BT. Prolonged high-fat diet induces gradual and fat depot-specific DNA methylation changes in adult mice. Sci Rep 2017;7:43261. https://doi.org/10.1038/srep43261

[65] Perfilyev A, Dahlman I, Gillberg L, Rosqvist F, Iggman D, Volkov P, Nilsson E, Risérus U, Ling C. Impact of polyunsaturated and saturated fat overfeeding on the DNA-methylation pattern in human adipose tissue: a randomized controlled trial. Am J Clin Nutr 2017;105:991-1000. https://doi.org/10.3945/ajcn.116.143164

[66] Aguirre L, Fernández-Quintela A, Arias N, Portillo M. Resveratrol: Anti-Obesity Mechanisms of Action. Molecules 2014;19:18632-55. https://doi.org/10.3390/molecules191118632

[67] Nettore IC, Rocca C, Mancino G, Albano L, Amelio D, Grande F, Puoci F, Pasqua T, Desiderio S, Mazza R, Terracciano D, Colao A, Bèguinot F, Russo GL, Dentice M, Macchia PE, Sinicropi MS, Angelone T, Ungaro P. Quercetin and its derivative Q2 modulate chromatin dynamics in adipogenesis and Q2 prevents obesity and metabolic disorders in rats. J Nutr Biochem 2019;69:151-62. https://doi.org/10.1016/j.jnutbio.2019.03.019

[68] Fortunato IM, dos Santos TW, Ferraz LFC, Santos JC, Ribeiro ML. Effect of Polyphenols Intake on Obesity-Induced Maternal Programming. Nutrients 2021;13:2390. https://doi.org/10.3390/nu13072390

[69] Moon H-S, Chung C-S, Lee H-G, Kim T-G, Choi Y-J, Cho C-S. Inhibitory Effect of (−)-Epigallocatechin-3-Gallate on Lipid Accumulation of 3T3-L1 Cells**. Obesity 2007;15:2571-82. https://doi.org/10.1038/oby.2007.309

[70] Chan CY, Wei L, Castro-Muñozledo F, Koo WL. (−)-Epigallocatechin-3-gallate blocks 3T3-L1 adipose conversion by inhibition of cell proliferation and suppression of adipose phenotype expression. Life Sci 2011;89:779-85. https://doi.org/10.1016/j.lfs.2011.09.006

[71] Aggarwal R, Jha M, Shrivastava A, Jha AK. Natural compounds: Role in reversal of epigenetic changes. Biochem 2015;80:972-89. https://doi.org/10.1134/S0006297915080027

[72] Khan MA, Hussain A, Sundaram MK, Alalami U, Gunasekera D, Ramesh L, Hamza A, Quraishi U. (-)-Epigallocatechin-3-gallate reverses the expression of various tumor-suppressor genes by inhibiting DNA methyltransferases and histone deacetylases in human cervical cancer cells. Oncol Rep 2015;33:1976-84. https://doi.org/10.3892/or.2015.3802

[73] Vacca RA, Valenti D, Caccamese S, Daglia M, Braidy N, Nabavi SM. Plant polyphenols as natural drugs for the management of Down syndrome and related disorders. Neurosci Biobehav Rev 2016;71865-77. https://doi.org/10.1016/j.neubiorev.2016.10.023

[74] Ergoren MC, Paolacci S, Manara E, Dautaj A, Dhuli K, Anpilogov K, Camilleri G, Suer HK, Sayan M, Tuncel G, Sultanoglu N, Farronato M, Tartaglia GM, Dundar M, Farronato G, Gunsel IS, Bertelli M, Sanlidag T. A pilot study on the preventative potential of alpha-cyclodextrin and hydroxytyrosol against SARS-CoV-2 transmission. Acta Biomed 2020:911-7. https://doi.org/10.23750/abm.v91i13-S.10817

[75] Paolacci S, Ergoren MC, De Forni D, Manara E, Poddesu B, Cugia G, Dhuli K, Camilleri G, Tuncel G, Kaya Suer H, Sultanoglu N, Sayan M, Dundar M, Beccari T, Ceccarini MR, Gunsel IS, Dautaj A, Sanlidag T, Connelly ST, Tartaglia GM, Bertelli M. In vitro and clinical studies on the efficacy of α-cyclodextrin and hydroxytyrosol against SARS-CoV-2 infection. Eur Rev Med Pharmacol Sci 2021;25:81-9. https://doi.org/10.26355/eurrev_202112_27337

[76] Sirianni R, Chimento A, De Luca A, Casaburi I, Rizza P, Onofrio A, Iacopetta D, Puoci F, Andò S, Maggiolini M, Pezzi V. Oleuropein and hydroxytyrosol inhibit MCF-7 breast cancer cell proliferation interfering with ERK1/2 activation. Mol Nutr Food Res 2010;54:833-40. https://doi.org/10.1002/mnfr.200900111

[77] Rosignoli P, Fuccelli R, Sepporta MV, Fabiani R. In vitro chemo-preventive activities of hydroxytyrosol: the main phenolic compound present in extra-virgin olive oil. Food Funct 2016;7:301-7. https://doi.org/10.1039/C5FO00932D

[78] Román GC, Jackson RE, Reis J, Román AN, Toledo JB, Toledo

E. Extra-virgin olive oil for potential prevention of Alzheimer disease. Rev Neurol (Paris) 2019;175:705-23. https://doi.org/10.1016/j.neurol.2019.07.017

[79] Wang P, Yamabe N, Hong CJ, Bai HW, Zhu BT. Caffeic acid phenethyl ester, a coffee polyphenol, inhibits DNA methylation in vitro and in vivo. Eur J Pharmacol 2020;887:173464. https://doi.org/10.1016/j.ejphar.2020.173464

[80] Cione E, La Torre C, Cannataro R, Caroleo MC, Plastina P, Gallelli L. Quercetin, Epigallocatechin Gallate, Curcumin, and Resveratrol: From Dietary Sources to Human MicroRNA Modulation. Molecules 2019;25:63. https://doi.org/10.3390/molecules25010063

[81] Wang S wei, Sheng H, Bai Y feng, Weng Y yuan, Fan X yu, Zheng F, Fu J qi, Zhang F. Inhibition of histone acetyltransferase by naringenin and hesperetin suppresses Txnip expression and protects pancreatic β cells in diabetic mice: Naringenin and hesperetin protect pancreatic β cells. Phytomedicine 2021;88:153454. https://doi.org/10.1016/j.phymed.2020.153454

[82] Kocabas Ş, Sanlier N. A comprehensive overview of the complex relationship between epigenetics, bioactive components, cancer, and aging. Crit Rev Food Sci Nutr 2021;0:1-13. https://doi.org/10.1080/10408398.2021.1986803

[83] Lee YM, Yoon Y, Yoon H, Park HM, Song S, Yeum KJ. Dietary anthocyanins against obesity and inflammation. Nutrients 2017;9:1-15. https://doi.org/10.3390/nu9101089

[84] Persico G, Casciaro F, Marinelli A, Tonelli C, Petroni K, Giorgio M. Comparative analysis of histone h3k4me3 distribution in mouse liver in different diets reveals the epigenetic efficacy of cyanidin-3-o-glucoside dietary intake. Int J Mol Sci 2021;22(12). https://doi.org/10.3390/ijms22126503

[85] Cappellini F, Marinelli A, Toccaceli M, Tonelli C, Petroni K. Anthocyanins: From Mechanisms of Regulation in Plants to Health Benefits in Foods. Front Plant Sci 2021;12. https://doi.org/10.3389/fpls.2021.748049

[86] Hsieh C-J, Kuo P-L, Hsu Y-C, Huang Y-F, Tsai E-M, Hsu Y-L. Arctigenin, a dietary phytoestrogen, induces apoptosis of estrogen receptor-negative breast cancer cells through the ROS/p38 MAPK pathway and epigenetic regulation. Free Radic Biol Med 2014:67159-70. https://doi.org/10.1016/j.freeradbiomed.2013.10.004

[87] Cui Y, Lu C, Liu L, Sun D, Yao N, Tan S, Bai S, Ma X. Reactivation of methylation-silenced tumor suppressor gene p16INK4a by nordihydroguaiaretic acid and its implication in G1 cell cycle arrest. Life Sci 2008;82:247-55. https://doi.org/10.1016/j.lfs.2007.11.013

[88] Jiang A, Wang X, Shan X, Li Y, Wang P, Jiang P, Feng Q. Curcumin Reactivates Silenced Tumor Suppressor Gene RARβ by Reducing DNA Methylation. Phyther Res 2015;29:1237-45. https://doi.org/10.1002/ptr.5373

[89] Bhat A, Mahalakshmi AM, Ray B, Tuladhar S, Hediyal TA, Manthiannem E, Padamati J, Chandra R, Chidambaram SB, Sakharkar MK. Benefits of curcumin in brain disorders. BioFactors 2019;45:666-89. https://doi.org/10.1002/biof.1533

[90] Meeran SM, Patel SN, Tollefsbol TO. Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines. PLoS One 2010;5(7). https://doi.org/10.1371/journal.pone.0011457

[91] Myzak MC, Dashwood WM, Orner GA, Ho E, Dashwood RH. Sulforaphane inhibits histone deacetylase in vivo and suppresses tumorigenesis in Apc min mice. FASEB J 2006;20:506-8. https://doi.org/10.1096/fj.05-4785fje

[92] Myzak MC, Karplus PA, Chung FL, Dashwood RH. A novel mechanism of chemoprotection by sulforaphane: Inhibition of histone deacetylase. Cancer Res 2004;64:5767-74. https://doi.org/10.1158/0008-5472.CAN-04-1326

[93] Wong CP, Hsu A, Buchanan A, Palomera-Sanchez Z, Beaver LM, Houseman EA, Williams DE, Dashwood RH, Ho E. Effects of sulforaphane and 3,3′-diindolylmethane on genome-wide promoter methylation in normal prostate epithelial cells and prostate cancer cells. PLoS One 2014;9(1). https://doi.org/10.1371/journal.pone.0086787

[94] Schepici G, Bramanti P, Mazzon E. Efficacy of sulforaphane in neurodegenerative diseases. Int J Mol Sci 2020;21:1-26. https://doi.org/10.3390/ijms21228637

[95] Zhao F, Zhang J, Chang N. Epigenetic modification of Nrf2 by sulforaphane increases the antioxidative and anti-inflammatory capacity in a cellular model of Alzheimer's disease. Eur J Pharmacol 2018;824:1-10. https://doi.org/10.1016/j.ejphar.2018.01.046

[96] Caradonna F, Consiglio O, Luparello C, Gentile C. Science and healthy meals in the world: Nutritional epigenomics and nutrigenetics of the mediterranean diet. Nutrients 2020;12:1-23. https://doi.org/10.3390/nu12061748

[97] Mansouri N, Alivand MR, Bayat S, Khaniani MS, Derakhshan SM. The hopeful anticancer role of oleuropein in breast cancer through histone deacetylase modulation. J Cell Biochem 2019;120:17042-9. https://doi.org/10.1002/jcb.28965

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How to cite this article: Kenanoglu S, Nuriye Gokce N, Akalin H, Ergoren MC, Beccari T, Bertelli M, Dundar M. Implication of the Mediterranean diet on the human epigenome. J Prev Med Hyg 2022;63(suppl.3):E44-E55. https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2746