Review Article **Open Access**

The epigenetic impact of daily diet food choices on human health and chronic diseases

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Submission Date: September 13th, 2024; **Acceptance Date:** October 20th, 2024; **Publication Date**: October 24th, 2024

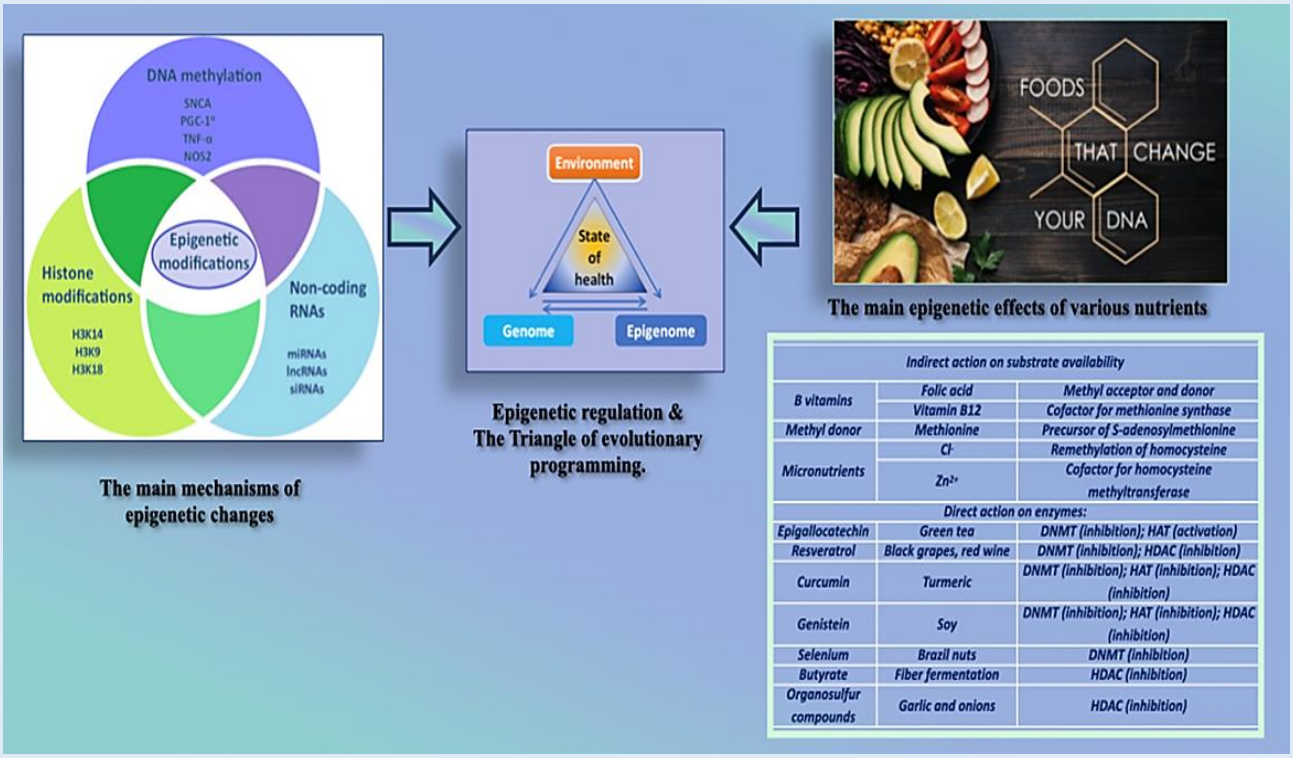
Please cite this article as: Yesayan A. H., Chetta M., Babayan B. G., Yesayan T. A., Esoyan S. S., Sevoyan G. G. The epigenetic impact of daily diet food choices on human health and chronic diseases. *Functional Foods in Health and Disease* 2024; 14(10). DOI: https://doi.org/10.31989/ffhd.v14i10.1464

ABSTRACT

Nutrition, certain lifestyle behaviors (smoking, drug, alcohol addictions, etc.) and environment all contribute to cancer and other lines development. Similarly, epigenetic pathways are known to occur at the intersection between the generally reversible effects of lifestyle or ecological factors and the irreversible alterations that explain numerous diseases. Chemoprevention is the process of intervening in the epigenome to mitigate the detrimental effects of environmental factors or certain lifestyles before they lead to significant consequences. DNA is permanently exposed to various substances modifying both its genetic and epigenetic configuration. It's controlled by various agents (methyl donors, sophisticated enzymes, etc.). Pesticides, artificial food additives, drugs and environmental toxins penetrating the placenta, can result in developmental program alterations and epigenetic changes in a fetus.

In nutrition context, the research revealed that several foods can alter epigenetic markers. Some vitamins may alter DNA methylation patterns and histone alterations, possibly influencing gene expression and disease risk. Thus, dietary treatments may provide an epigenetic regulation, emphasizing nutrition role in preserving health and preventing illness via epigenetics

Keywords: human epigenetics, epigenetic regulation of diseases, daily food ration, healthy food



Graphical Abstract: The Epigenetic Impact of Daily Diet Food Choices on Human Health and Chronical Diseases

INTRODUCTION:

Epigenetic pathways are now well-recognized as a critical connection between the mostly reversible impacts of lifestyle or environmental factors and the permanent alterations that cause numerous diseases [1-2]. Diet, lifestyle choices (smoking, alcohol usage) and environmental variables can all have a substantial impact on development of diseases, (cancers, diabetes, cardiovascular diseases (CVDs), etc.). Epigenetics and nutrition became critical for understanding of origin and progression of numerous chronic illnesses [3-5]. Food contains nutrients and bioactive chemicals that can alter epigenetic processes: DNA methylation, histone modification, non-coding RNA (ncRNA) production, as well as reduce cellular stress and damage. Different substances, ranging from methyl donors to intricate enzymes are involved in epigenetic control (EC). They provide functional footprints to genome, activating or deactivating genes [6-8]. These changes, brought on by drugs, pesticides, environmental pollutants, may pass through the placenta and affect a fetus's development, frequently through major epigenetic modifications, particularly in the early stages of development. The environment, genome and epigenome together define the idea of “developmental programming” (Fig. 1.) [9-10].

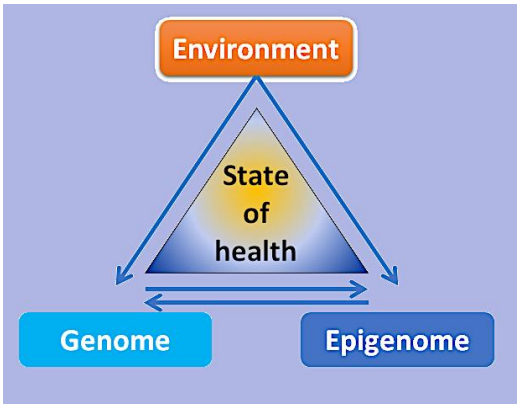


Fig. 1. Triangle of evolutionary programming.
(The evolutionary programing theory postulates that health is defined by the environment, genome and epigenome interaction what ensure the adaptation).

The factors encountered during pregnancy affect a person's vulnerability to diseases in future. A typical example of a disorder impacted by developmental programming is metabolic syndrome (high blood pressure, obesity, high triglyceride levels, low HDL (High Density lipoproteins) levels, hyperglycemia, predispositions to CVD and type 2 diabetes (T2D)) [11-13]. The hypothesis that unfavorable circumstances (low birth weight, temperatures, oxygen levels, mother's limited nutrition) might interact with hereditary variables to raise the risk of illness in adulthood is supported by epidemiological studies [14]. Nonetheless, there have been some discrepancies found in data from animal models or *in vitro* research, where the length of therapy and its form of administration may have affected the outcomes [15-17]. However, in several examples it's widely acknowledged that certain dietary elements impact the epigenetic markers concerning nutrition. Vitamins B_9, B_{12}, and polyphenols affect DNA methylation and histone modifications, which affect gene expression associated with specific disorders [18-21]. Thus, the nutrition plays a crucial role in preserving health via epigenetic pathways. It suggests that dietary interventions, during pregnancy, might offer a potential strategy of epigenetic processes modification for the prevention of diseases [22-23].

This review investigates how epigenetic markers are changed by everyday food decisions, which can either increase or decrease the risk of chronic illnesses and affect human health.

Methodology: Several methods are available for epigenome studies. Pyrosequencing and whole-genome sequencing are used for quantitative studies of DNA methylation. Histone modifications can be investigated by chromatin immunoprecipitation [24]. Their acetylation and methylation, are detected by specific antibodies. Global histone modifications can be quantified by mass spectrometry and Western blotting. miRNAs and lncRNAs are studied by RNA sequencing using next generation technologies and quantitative PCR. Epigenome-wide association studies can detect genome-wide epigenetic changes caused by environmental factors [25-26]. Global epigenetic markers are assessed by enzyme-linked immunosorbent assay (ELISA) and chromatography. Epi-exposure mapping is used for to trac the exposure-related epigenetic alterations [27].

Overview of Epigenetic Mechanisms: The term "epigenetic regulation" describes a group of mechanisms that manage the gene expression (including DNA replication and repair genes) without changing the

underlying DNA sequence. These processes are impacted by both hereditary and environmental variables and are essential for regular cellular activities. Histone modifications, ncRNA regulation, DNA methylation and demethylation, are crucial for EC [28].

DNA methylation is the well-studied mechanism, involving Cyt methylation in CpG (or CG) dinucleotides (where Cyt is followed by Gua (guanine)) of promoters. That mostly suppresses genes. Cancer, heart and neurological problems are linked to aberrant DNA methylation patterns in early stages. The nutrition effect on DNA methylation is caused by methionine (Met), B_{12}, folate (or vitamin M or B_9) [29-30]. They define hypo- or hypermethylation, which disturb normal gene expression and accelerate the onset of illness. Histones are the hubs around which DNA is coiled to create chromatin. Thus, their phosphorylation, methylation, and acetylation are essential for chromatin remodeling and gene expression. Histone acetylation usually leads to chromatin increased flexibility, which improves gene expression, while deacetylation condenses the chromatin and frequently silences genes [31-33]. Histone alterations are being affected by plant-derived polyphenols. By acting as histone deacetylase (HDAC) inhibitors, they increase tumor suppressor genes (TSG) expression and decrease cancer risks. Lastly ncRNAs (lncRNAs) are important post-transcriptional regulators of gene expression, and they include lncRNAs and microRNAs (miRNAs). They act by attaching to messenger RNA (mRNA) and either increasing or decreasing mRNA translation [34-36]. Cancer, MS, chronical inflammations, etc. are related to miRNA and lncRNA expression regulation. ncRNA expression is influenced by certain plant-derived polyunsaturated fatty acids (PUFAs). They impact the miRNA production, what affects the metabolism regulation [37-38].

The Role of Diet in Epigenetic Regulation: Nutrients and bioactive dietary ingredients are important for epigenetic regulation (table 1) [39].

Table 1. The nutrients main epigenetic effects

Indirect action on substrate availability		
B vitamins	B_9	Methyl acceptor/donor
	B_{12}	Met synthase cofactor
Methyl donor	Met	Precursor of S-adenosyl-Met
Micronutrients	Cl^-	homo-Cys (homocysteine) remethylation
	Zn^{2+}	homo-Cys methyltransferase cofactor
Direct action on enzymes:		
Epigallocatechin	Green tea	$DNMT_{inhibition}$; $HAT_{activation}$
Resveratrol	Black grapes, red wine	$DNMT_{inhibition}$; $HDAC_{inhibition}$
Curcumin	Turmeric	$DNMT_{inhibition}$; $HAT_{inhibition}$; $HDAC_{inhibition}$
Genistein	Soy	$DNMT_{inhibition}$; $HAT_{inhibition}$; $HDAC_{inhibition}$
Selenium	Brazil nuts	$DNMT_{inhibition}$
Butyrate	Fibers	$HDAC_{inhibition}$
Organosulfur compounds	Garlic, onions	$HDAC_{inhibition}$

Met, B_{12}, and B_9 as methyl-donors are important for one-carbon groups metabolism and ensure DNA Cyt methylation, what is critical for EC. Global DNA hypomethylation, as cancer risk factor, can result from a lack in these nutrients. Pogribny et al. in 2008 showed that hypomethylation, activating the oncogenes and silencing TSG, is a result of insufficient methyl donors.

Hypomethylation is linked to neurological pathologies and CVDs. The diet high in these vitamins is essential for avoiding the mentioned illnesses [41-43]. Polyphenols are the components of tea, fruits, vegetables, etc. and are important for EC of histone modifications. Their acetylation and methylation are influenced by polyphenols (bioflavonoids or vitamin P group), phenolic acids, stilbenes, which in turn affects gene expression. Resveratrol inhibits HDACs. It's mostly found in grape products. TSG are activated when resveratrol increases histone acetylation through the inhibition of HDACs [44-46]. Lagouge et al.'s (2006) research revealed that its capacity to raise histone acetylation accounts for some of anti-tumor effects [47]. The effects of green tea's catechins, were shown by Fang et al. (2003) and Weinstein et al.'s (2007) for histone methylation, which may decrease cancer risks. However, the green tea anticancerogenic properties research remain actual due to the absence of regular data about the overconsumption and negative effects of it on stomac cancer [48-50]. miRNAs regulate omega-3 and omega-6 fatty acids (FA) metabolism, what is important for inflammation, lipid metabolism and insulin sensitivity. Fish and seed oils include omega-3 PUFAs, which downregulate pro-inflammatory miRNAs, decreasing chronical inflammation, CVDs, etc. [51]. Omega-3 FA decrease inflammation, improve lipid profiles and insulin sensitivity. The diets high in omega-6 PUFAs are related to increased pro-inflammatory miRNAs, which contribute to chronic inflammations, cancer and CVD. Maintaining an optimum mix of omega-3 and omega-6 FA is critical for controlling miRNA expression and lowering the mentioned illness risks [52-55].

Epigenetics and Cancer: Epigenetic alterations are often changed in malignancies, influencing tumor formation and progression [56]. Importantly, nutrition influences these epigenetic changes and has a potential for both cancer prevention and therapy. Often cancers are linked to DNA hypermethylation (silences TSG) and hypomethylation (activates oncogenes). Abnormalities in it can affect cellular growth [57-59]. B_9, B_{12} and SAM (S-adenosyl-Met) are important for DNA methylation (Fig. 2) [60].

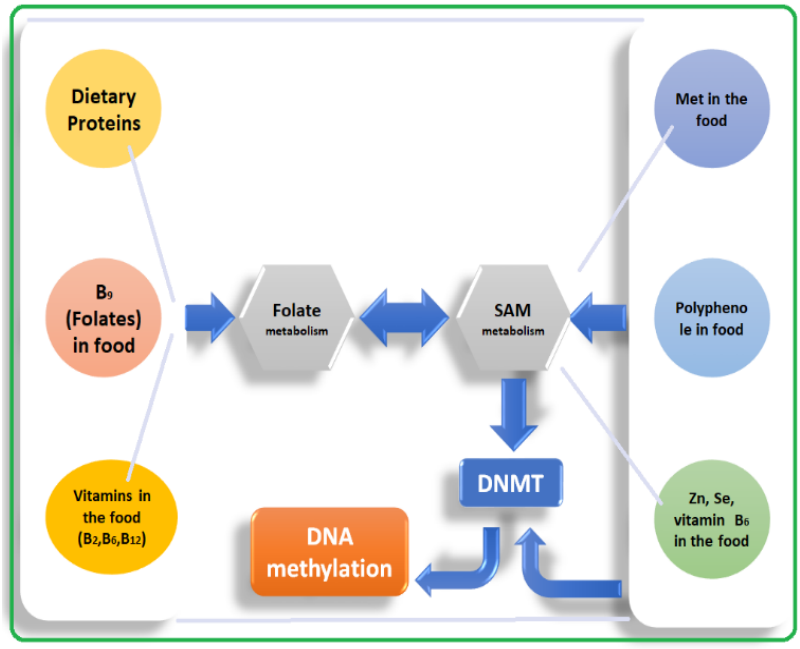


Fig. 2. Effect of diet on DNA methylation.

Both low and high levels of them are related to cancer risks. Inadequate B_9 consumption is linked to increased risk of colon cancer, mainly due to oncogene hypomethylation. B_9 overconsumption promotes cancer growth by hypermethylating and silencing of TSG [61].

Cancer-preventive properties of plant-derived polyphenols are associated with their capacity to impact histone changes [62]. These compounds (including resveratrol and epigallocatechin gallate or EGCG from green tea), have been demonstrated to block HDACs, resulting in the reactivation of tumor suppressor gene. They inhibit HDACs, which induces histone acetylation gene expression activation. Beyond the histone modifications, polyphenols influence DNA methylation: curcumin, a polyphenol of turmeric, has been demonstrated to demethylase tumor suppressor gene promoters, causing them to reactivate in cancer cells [63-65]. Thus, polyphenols affect numerous epigenetic pathways to achieve anticancer activity. Dysregulated miRNA expression contributes to suppression of TSG or the activation of oncogenes. It is associated with different types of cancer [66]. Omega-3 PUFAs and polyphenols, might modulate miRNA expression, potentially influencing cancer-related pathways. They affect inflammation miRNAs expression and control cell proliferation. Polyphenols EGCG and resveratrol can affect miRNA expression, targeting pathways implicated in tumor suppression and cancer development [67-69].

Epigenetics and Cardiovascular Diseases (CVD): CVD is the leading cause of mortality globally. The research is increasingly highlighting the significance of epigenetic pathways in its progression. CVD is impacted by both hereditary and environmental factors, including food. Epigenetic changes, play critical roles in pathophysiology of CVD, including atherosclerosis, hypertension, and heart failure. Understanding these mechanisms may assist to create better preventative and treatment methods. Aberrant DNA methylation patterns are increasingly thought to contribute to CVD risk. Hypermethylation of lipid metabolism and inflammation genes are linked to increased risks of atherosclerosis. Hypermethylation of genes affecting cholesterol transport or inflammatory cytokines can accelerate the vascular atherosclerotic plaques development [70-71].

Vitamins B_9 and B_{12} can offer protection against CVD, because they are required to maintain normal methylation patterns. A proper intake of them reduces homo-Cys (homocysteine) levels, a well-known risk factor for CVD [72]. Homo-Cys increased level can harm the blood vessels, but methyl-donor meals can help prevent this, potentially decreasing CVD risks [73]. miRNAs also, are important for CVD development epigenetic regulation. They affect the lipid metabolism, inflammation, and endothelial function, all of which are important for cardiovascular health [74]. Dysregulated miRNA expression is linked to CVDs. The studies reveal that food might influence miRNA levels, providing a possible treatment strategy. For example, omega-3 PUFAs contained of fish oil reduce the expression of miRNAs associated with inflammation and lipid metabolism, potentially decreasing the risk of CVD. Omega-3s affect the expression of miR-33 (family of miRNA precursors, which are processed by the Dicer enzyme to give mature miRNAs) effecting the cholesterol regulation, improving lipid profiles and lowering atherosclerotic risks [75-76].

In addition to omega-3s, resveratrol and quercetin of apples, onions, and tea, have cardio-protective effects by modulating miRNA expression. Resveratrol upregulates miRNAs that increases the endothelial function and decreases the inflammation, regulating blood vessel functions. Quercetin impacts the miRNA expression, regulating the vascular smooth muscle cells, hence preventing arterial stiffness and other hypertension-related disorders [77-79]. Hypertension is a

major risk factor for heart failure and other CVDs. Epigenetic modulation is critical for blood pressure management, because DNA methylation patterns are linked to hypertension development [80]. In hypertensive individuals, altered methylation has resulted in persistently high blood pressure due to epigenetic modifications in genes involved in renin-angiotensin system (RAS) balance, regulating the blood pressure, fluid modified vascular tone and control, such as like the salt balance [81]. Antioxidants and salt intake are two dietary variables that affect epigenetic modifications. An excessively salty diet led to aberrant methylation of Vascular Endothelial Growth Factor (VEGF), what raises blood pressure. Conversely, diets rich in omega-3 FA and polyphenols may protect against these epigenetic modifications causing hypertension [83-85].

Epigenetics and Metabolic Disorders: Metabolic disorders (obesity, T2D), etc.), are multifactorial illnesses caused by the mix of hereditary and environmental variables, with epigenetic changes playing a critical role. According to recent study, people with metabolic diseases more frequently have different DNA methylation patterns than people who are healthy. For example, hypermethylation of genes involved in insulin signaling and glucose metabolism (GM) are linked to higher risk of T2D [84]. DNA methylation alterations in PPARγ (Peroxisome Proliferator-Activated Receptor Gamma) and IRS1 (Insulin receptor substrate 1), involved in adipocyte development and insulin signaling are linked to insulin sensitivity and metabolic abnormalities [85]. Adequate consumption of B_9, B_{12} helps maintain normal methylation patterns, which control GM. Methyl donor-rich diet can enhance insulin sensitivity and lower T2D risks [86]. Dietary therapies targeting epigenetic modifications may aid in managing inflammation and metabolic health, since hypomethylation of inflammatory genes like TNF-α has been linked to obesity [87]. Histone changes control Glc homeostasis, lipid metabolism, insulin sensitivity, etc.: acetylation stimulates gene expression by relaxing chromatin structure and allowing transcription factors to access DNA. In case of GM genes, it can improve insulin sensitivity and Glc absorption in tissues. FOXO1 (Forkhead box O1) is also involved in gluconeogenesis and insulin signaling. Its histone methylation led to increased Glc production and insulin resistance. Histone acetylation of other genes can enhance the lipid synthesis and led to fatty liver disease or dyslipidemia [88-89]. Resveratrol and curcumin have been demonstrated to alter histone acetylation and methylation, resulting in better lipid metabolism and anti-inflammatory actions [90-91]. MiRNAs can either increase or decrease the expression insulin signaling, fat storage, and GM genes. Dysregulation of miRNAs (miR-103 and miR-107) is associated with insulin resistance and T2D. In these regards, omega-3 FA reduce pro-inflammatory miRNAs associated to insulin resistance [92]. Quercetin and EGCG can also alter miRNA expression, resulting in anti-inflammatory and metabolism-regulating beneficial effects [93].

CONCLUSION

Food-based nutrients and bioactive substances can alter important epigenetic processes, including histone modification, DNA methylation, and ncRNA expression, which in turn affects gene expression related to health risks. This review provides a ground-breaking investigation of how dietary choices affect epigenetic pathways, contributing significantly to our understanding of nutrition's involvement in chronic illness prevention and management. It explains how foods interact with essential epigenetic processes to influence gene expression. It also dives into developing topics, such as the effect of dietary components on miRNAs, and offers

the idea of dietary interventions throughout important life phases (pregnancy, etc.) as the potential innovative technique of preventive medicine. The review emphasizes prospective research priorities (personalized nutrition, nutrient-epigenome interactions, etc.). Finally, this finding paves the way for development of nutritional interventions and therapeutic techniques for diseases influenced by epigenetics, such as cancer and metabolic disorders.

Abbreviations: CVD, Cardiovascular disease; Cyt, cytosine; EGCG, epigallocatechin gallate; ELISA, enzyme-linked immunosorbent assay; FA, fatty acids; FOXO1, Forkhead box O1; Glc, glucose; GM, glucose metabolism; GLUT4, insulin-regulated glucose transporter 4**;** Gua, guanine; HDACs, histone deacetylases; HDL, High Density lipoproteins; IRS1, Insulin receptor substrate 1**;** homo-Cys, homocysteine; lncRNAs, Long non-coding RNAs; Met, Methionine; MS, metabolic syndrome; mRNA, messenger RNA; miRNA, microRNA; ncRNA, non-coding RNA; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma; RNA, ribonucleic acid; PUFAs, polyunsaturated FA, PUFAs; SAM, S-adenosylmethionine; SREBP1, Sterol regulatory element-binding transcription factor 1; TSG, tumor suppressor genes; T2D, type 2 diabetes; VEGF, Vascular Endothelial Growth Factor.

Author's Contributions: All authors contributed to this study. No competing interests were disclosed.

Acknowledgments: We're thankful to all staff of laboratory of Applied Biology and Ecology, Research Institute of Biology, YSU.

REFERENCES

1. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet. 2007, 8(4):253-262. DOI: https://doi.org/10.1038/nrg2045
2. Feinberg AP, Tycko B. The history of cancer epigenetics. Nat Rev Cancer. 2004, 4(2):143-153. DOI: https://doi.org/10.1038/nrc1279
3. Jones PA, Baylin SB. The epigenomics of cancer. Cell. 2007, 128(4):683-92. DOI: https://doi.org/10.1016/j.cell.2007.01.029
4. Elmallah MIY, Micheau O. Epigenetic Regulation of TRAIL Signaling: Implication for Cancer Therapy. Cancers (Basel). 2019, 11(6):850. DOI: https://doi.org/10.3390%2Fcancers11060850
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011, 144 (5):646-674. DOI: https://doi.org/10.1016/j.cell.2011.02.013
6. Lu Q, Liu X, Liu R. The role of dietary polyphenols in the regulation of DNA methylation. Nutrients. 2016, 8(5):287. DOI: https://doi.org/10.3390%2Fantiox9080691
7. Yang X, Han H, De Carvalho DD. Gene body methylation can alter gene expression and is a therapeutic target in cancer. Cancer Cell. 2014, 26(4):577-590. DOI: https://doi.org/10.1016/j.ccr.2014.07.028
8. Berezovsky E, Kohn E, Britzi M, Efreim S, Berlin M, Oppenheimer S, Avitsur R, Agajany N, Berkovitch M, Sheinberg R. Possible associations between prenatal exposure to environmental pollutants and neurodevelopmental outcome in children. Reprod Toxicol. 2024, 128:108658. DOI: https://doi.org/10.1016/j.reprotox.2024.108658
9. Nguyen AH, Murrin E, Moyo A, Sharma G, Sullivan SA, Maxwell GL, Kennedy JLW, Saad AF. Ischemic heart disease in pregnancy: a practical approach to management. Am J Obstet Gynecol MFM. 2024, 6(3):101295. DOI: https://doi.org/10.1016/j.ajogmf.2024.101295
10. Matovelle P, Oliván-Blázquez B, Domínguez-García M, Casado-Vicente V, Pascual de la Pisa B, Magallón-Botaya R. Health Outcomes for Older Patients with Chronic Diseases During the First Pandemic Year. Clin Interv Aging. 2024, 19:385-397. DOI: https://doi.org/10.2147/cia.s444716
11. Robertson OC, Marceau K, Moding KJ, Knopik VS, Developmental pathways linking obesity risk and early puberty: The thrifty phenotype and fetal overnutrition hypotheses, Developmental Review, 2022, 66:101048. DOI: https://doi.org/10.1016/j.dr.2022.101048
12. Silva-Ochoa AD, Velasteguí E, Falconí IB, et al. Metabolic syndrome: Nutri-epigenetic cause or consequence? Heliyon. 2023, 9(11):e21106. DOI: https://doi.org/10.1016%2Fj.heliyon.2023.e21106
13. Laakso M, Fernandes Silva L. Genetics of Type 2 Diabetes: Past, Present, and Future. Nutrients. 2022;14(15):3201.

DOI: https://doi.org/10.3390%2Fnu14153201

14. Faa G, Fanos V, Manchia M, Van Eyken P, Suri JS, Saba L. The fascinating theory of fetal programming of adult diseases: A review of the fundamentals of the Barker hypothesis. J Public Health Res. 2024, 13(1):22799036241226817. DOI: https://doi.org/10.1177%2F22799036241226817
15. Cheng M, Conley D, Kuipers T, Li C, Ryan CP, Taeubert MJ, Wang S, Wang T, Zhou J, Schmitz LL, Tobi EW, Heijmans B, Lumey LH, Belsky DW. Accelerated biological aging six decades after prenatal famine exposure. Proc Natl Acad Sci USA. 2024, 121(24):e2319179121. DOI: https://doi.org/10.1073/pnas.2319179121
16. Zhu J, Yang Y, Li L, Tang J, Zhang R. DNA methylation profiles in cancer: functions, therapy, and beyond. Cancer Biol Med. 2023, 21(2):111-116. DOI: https://doi.org/10.20892%2Fj.issn.2095-3941.2023.0403
17. Morita S, Horii T, Hatada I. Optimized Protocol for the Regulation of DNA Methylation and Gene Expression Using Modified dCas9-SunTag Platforms. Methods Mol Biol. 2024, 2842:155-165. DOI: https://doi.org/10.1007/978-1-0716-4051-7_7
18. Melnik B.C., Schmitz G., DNA methyltransferase1-targeting miRNA-148a of dairy milk: a potential bioactive modifier of the human epigenome. Functional Foods in Health and Disease 2017; 7(9);671-687. DOI: https://doi.org/10.31989/ffhd.v7i9.379
19. Bekdash RA. Epigenetics, Nutrition, and the Brain: Improving Mental Health through Diet. Int J Mol Sci. 2024;25(7):4036. DOI: https://doi.org/10.3390%2Fijms25074036
20. Mirisola MG. The Nutriepigenome. Genes (Basel). 2023, 14(11):1997. DOI: https://doi.org/10.3390%2Fgenes14111997
21. Tspnetsyan H., Pepoyan E., Pepoyan A., Abrahamyan S. Marketability level of potato in Armenia: Potato functional properties. Functional Foods in Health and Disease 2023; 13(5): 268-283 DOI: https://www.doi.org/10.31989/ffhd.v13i5.1103
22. Michels KB, Binder AM. Impact of folic acid supplementation on the epigenetic profile in healthy unfortified individuals - a randomized intervention trial. Epigenetics. 2024, 19(1):2293410. DOI: https://doi.org/10.1080%2F15592294.2023.2293410
23. Yu, X., Zhao, H., Wang, R. et al. Cancer epigenetics: from laboratory studies and clinical trials to precision medicine. Cell Death Discov. 2024, 10:28. DOI: https://doi.org/10.1038/s41420-024-01803-z
24. Li Y. Modern epigenetics methods in biological research. Methods. 2021;187:104-113. DOI: https://doi.org/10.1016%2Fj.ymeth.2020.06.022
25. Al Balushi H, Zeinelabdin N. High-performance liquid chromatography for methylation detection. Epigenetics. 2017, 12(3):203-212. DOI: https://doi.org/10.1080/15592294.2017.1280956
26. Stein RA. Epigenetics and environmental exposures. J Epidemiol Community Health. 2012 Jan;66(1):8-13. DOI: https://doi.org/10.1136/jech.2010.130690
27. Liu Q, Ton J, Manavella PA, Komiya R, Zhai J. Focus on epigenetics. Plant Physiol. 2024,194(4):1925-1928. DOI: https://doi.org/10.1093%2Fplphys%2Fkiae104
28. Rasmi Y, Shokati A, Hassan A, et al. The role of DNA methylation in progression of neurological disorders and neurodegenerative diseases as well as the prospect of using DNA methylation inhibitors as therapeutic agents for such disorders. IBRO Neurosci Rep. 2022, 14:28-37. DOI: https://doi.org/10.1016%2Fj.ibneur.2022.12.002
29. Allison J, Kaliszewska A, Uceda S, Reiriz M, Arias N. Targeting DNA Methylation in the Adult Brain through Diet. Nutrients. 2021, 13(11):3979. DOI: https://doi.org/10.3390/nu13113979
30. Gurugubelli KR, Ballambattu VB. Perspectives on folate with special reference to epigenetics and neural tube defects. Reprod Toxicol. 2024, 125:108576. DOI: https://doi.org/10.1016/j.reprotox.2024.108576
31. Innis SM, Cabot RA. Chromatin profiling and state predictions reveal insights into epigenetic regulation during early porcine development. Epigenetics Chromatin. 2024, 17(1):16. DOI: https://doi.org/10.1186/s13072-024-00542-w
32. Eberharter A, Becker PB. Histone acetylation: a switch between repressive and permissive chromatin. Second in review series on chromatin dynamics. EMBO Rep. 2002, 3(3):224-229. DOI: https://doi.org/10.1093%2Fembo-reports%2Fkvf053
33. Bártová E. Epigenetic and gene therapy in human and veterinary medicine. Environ Epigenet. 2024, 10(1): dvae006. DOI: https://doi.org/10.1093/eep/dvae006
34. Good DJ. ncRNAs in Human Health and Diseases. Genes (Basel). 2023, 14(7):1429. DOI: https://doi.org/10.3390%2Fgenes14071429
35. Garrido-Palacios A, Rojas Carvajal AM, Núñez-Negrillo AM, Cortés-Martín J, Sánchez-García JC, Aguilar-Cordero MJ. MicroRNA Dysregulation in Early Breast Cancer Diagnosis: A

Systematic Review and Meta-Analysis. Int J Mol Sci. 2023, 24(9):8270. DOI: https://doi.org/10.3390/ijms24098270

36. GuttDayal S, Chaubey D, Joshi DC, Ranmale S, Pillai B. Noncoding RNAs: Emerging regulators of behavioral complexity. Wiley Interdiscip Rev RNA. 2024, 15(3):e1847. DOI: https://doi.org/10.1002/wrna.1847
37. Shiojima Y, Takahashi M, Kikuchi M, Akanuma M. Effect of ellagic acid on body fat and triglyceride reduction in healthy overweight volunteers: a randomized, double-blind, placebo-controlled parallel group study. Functional Foods in Health and Disease. 2020, 10(4): 180-194. DOI: https://doi.org/10.31989/ffhd.v10i4.702
38. Niculescu MD, Zeisel SH. Diet, methyl donors and DNA methylation: interactions between dietary folate, methionine and choline. J Nutr. 2002, 132(8 Suppl):2333S-2335S. DOI: https://doi.org/10.1093/jn/132.8.2333s
39. Van Vliet MM, Schoenmakers S, Gribnau J, Steegers-Theunissen RPM. The one-carbon metabolism as an underlying pathway for placental DNA methylation - a systematic review. Epigenetics. 2024, 19(1):2318516. DOI: https://doi.org/10.1080%2F15592294.2024.2318516
40. Choi SW, Mason JB. Folate status: effects on pathways of colorectal carcinogenesis. J Nutr. 2002, 132(8 Suppl):2413S-2418S. DOI: https://doi.org/10.1093/jn/132.8.2413s
41. Choi SW, Friso S. Modulation of DNA methylation by one-carbon metabolism: a milestone for healthy aging. Nutr Res Pract. 2023, 17(4):597-615. DOI: https://doi.org/10.4162%2Fnrp.2023.17.4.597
42. Kim YI Folate and colorectal cancer: an evidence-based critical review. Molecular Nutrition & Food Research, 2007, 51(3), 267-292. DOI: https://doi.org/10.1002/mnfr.200600191
43. Bié J, Sepodes B, Fernandes PCB, Ribeiro MHL. Polyphenols in Health and Disease: Gut Microbiota, Bioaccessibility, and Bioavailability. Compounds. 2023, 3(1):40-72. DOI: https://doi.org/10.3390/compounds3010005
44. Santos RA, Pessoa HR, Daleprane JB, de Faria Lopes GP, da Costa DCF. Comparative Anticancer Potential of Green Tea Extract and Epigallocatechin-3-gallate on Breast Cancer Spheroids. Foods. 2023, 13(1):64. DOI: https://doi.org/10.3390%2Ffoods13010064
45. Cao Y, Cui L, Tuo S, Liu H, Cui S. Resveratrol mediates mitochondrial function through the sirtuin 3 pathway to improve abnormal metabolic remodeling in atrial fibrillation. Eur J Histochem. 2024, 68(2):4004. DOI: https://doi.org/10.4081/ejh.2024.4004
46. Donohoe DR, Collins LB, Wali A, Bigler R, Sun W, Bultman SJ. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. Mol Cell. 2012, 48(4):612-26. DOI: https://doi.org/10.1016/j.molcel.2012.08.033
47. Isono Y, Watanabe H, Kumada M, Takara T, Iio S. Black tea decreases postprandial blood glucose levels in healthy humans and contains high-molecular-weight polyphenols that inhibit α-glucosidase and α-amylase *in vitro*: a randomized, double blind, placebo-controlled, crossover trial. Functional Foods in Health and Disease 2021, 11(5): 222-237. DOI: https://doi.org/10.31989/ffhd.v11i5.791
48. Li X, Yu C, Guo Y, et al. Association between tea consumption and risk of cancer: a prospective cohort study of 0.5 million Chinese adults. Eur J Epidemiol. 2019, 34(8):753-763. DOI: https://doi.org/10.1007%2Fs10654-019-00530-5
49. Wu MH, Liu JY, Tsai FL, et al. The adverse and beneficial effects of polyphenols in green and black teas *in vitro* and *in vivo*. Int J Med Sci. 2023, 20(10):1247-1255. DOI: https://doi.org/10.7150%2Fijms.85521
50. Kang JX, Weylandt KH. Modulation of inflammatory cytokines by omega-3 fatty acids. Subcell Biochem. 2008, 49:133-43. DOI: https://doi.org/10.1007/978-1-4020-8831-5_5
51. Fernández-Lázaro D, Arribalzaga S, Gutiérrez-Abejón E, Azarbayjani MA, Mielgo-Ayuso J, Roche E. Omega-3 Fatty Acid Supplementation on Post-Exercise Inflammation, Muscle Damage, Oxidative Response, and Sports Performance in Physically Healthy Adults-A Systematic Review of Randomized Controlled Trials. Nutrients. 2024, 16(13):2044. DOI: https://doi.org/10.3390%2Fnu16132044
52. Zhao M, Xiao M, Tan Q, Ji J, Lu F. Association between dietary omega-3 intake and coronary heart disease among American adults: The NHANES, 1999-2018. PLoS One. 2023,18(12):e0294861. DOI: https://doi.org/10.1371%2Fjournal.pone.0294861
53. El-Seweidy MM, Ali SI, Elsweify SE, Ali AA, Mashhour MM Omega3 fatty acids intake versus diclofenac in osteoarthritis induced in experimental rats.Functional Foods in Health and Disease 2017, 7(4);291-302. DOI: https://doi.org/10.31989/ffhd.v7i4.331
54. Bowen KJ, Harris WS, Kris-Etherton PM. Omega-3 Fatty Acids and Cardiovascular Disease: Are There Benefits?. Curr Treat Options Cardiovasc Med. 2016, 18(11):69. DOI: https://doi.org/10.1007%2Fs11936-016-0487-1

55. Kanwal R, Gupta S. Epigenetics and cancer. J Appl Physiol (1985). 2010, 109(2):598-605. DOI: https://doi.org/10.1152%2Fjapplphysiol.00066.2010
56. Hardy TM, Tollefsbol TO. Epigenetic diet: impact on the epigenome and cancer. Epigenomics. 2011, 3(4):503-518. DOI: https://doi.org/10.2217%2Fepi.11.71
57. Gu M, Ren B, Fang Y, et al. Epigenetic regulation in cancer. MedComm (2020). 2024, 5(2): e495. DOI: https://doi.org/10.1002%2Fmco2.495
58. Tsai HC, Baylin SB. Cancer epigenetics: linking basic biology to clinical medicine. Cell Res. 2011, 21(3):502-517. DOI: https://doi.org/10.1038%2Fcr.2011.24
59. Thabet RH, Alessa REM, Al-Smadi ZKK, et al. Folic acid: friend or foe in cancer therapy. Journal of International Medical Research. 2024, 52(1). DOI: http://doi:10.1177/03000605231223064
60. Pieroth R, Paver S, Day S, Lammersfeld C. Folate and Its Impact on Cancer Risk. Curr Nutr Rep. 2018, 7(3):70-84. DOI: https://doi.org/10.1007/s13668-018-0237-y
61. Seyoum Tola F. The concept of folic acid supplementation and its role in prevention of neural tube defect among pregnant women: PRISMA. Medicine (Baltimore). 2024, 103(19):e38154. DOI: https://doi.org/10.1097%2FMD.0000000000038154
62. Delcuve, G.P., Khan, D.H. & Davie, J.R. Roles of histone deacetylases in epigenetic regulation: emerging paradigms from studies with inhibitors. Clin Epigenet 4, 5 (2012). DOI: https://doi.org/10.1186/1868-7083-4-5 .
63. Kciuk M, Alam M, Ali N, et al. Epigallocatechin-3-Gallate Therapeutic Potential in Cancer: Mechanism of Action and Clinical Implications. Molecules. 2023, 28(13):5246. DOI: https://doi.org/10.3390%2Fmolecules28135246
64. Dufault RJ, Adler KM, Carpenter DO, Gilbert SG, Crider RA. Nutritional epigenetics education improves diet and attitude of parents of children with autism or attention deficit/hyperactivity disorder. World J Psychiatry. 2024, 14(1):159-178. DOI: https://doi.org/10.5498%2Fwjp.v14.i1.159
65. Borsoi FT, Neri-Numa IA, de Oliveira WQ, de Araújo FF, Pastore GM. Dietary polyphenols and their relationship to the modulation of non-communicable chronic diseases and epigenetic mechanisms: A mini-review. Food Chem (Oxf). 2022, 6:100155. DOI: https://doi.org/10.1016%2Fj.fochms.2022.100155
66. Billi M, De Marinis E, Gentile M, Nervi C, Grignani F. Nuclear miRNAs: Gene Regulation Activities. Int J Mol Sci. 2024, 25(11):6066. DOI: https://doi.org/10.3390%2Fijms25116066
67. Mandys V, Popov A, Gürlich R, et al. Expression of Selected miRNAs in Normal and Cancer-Associated Fibroblasts and in BxPc3 and MIA PaCa-2 Cell Lines of Pancreatic Ductal Adenocarcinoma. Int J Mol Sci. 2023, 24(4):3617. DOI: https://doi.org/10.3390%2Fijms24043617
68. Ivanova M, Moss EG. A temporal sequence of heterochronic gene activities promotes stage-specific developmental events in *Caenorhabditis elegans*. G3 (Bethesda). 2024, 14(8):jkae130. DOI: https://doi.org/10.1093/g3journal/jkae130
69. Kursvietiene L, Kopustinskiene DM, Staneviciene I, et al. Anti-Cancer Properties of Resveratrol: A Focus on Its Impact on Mitochondrial Functions. Antioxidants (Basel). 2023, 12(12):2056. DOI: https://doi.org/10.3390%2Fantiox12122056
70. Skinner MK. Environmental Epigenetics 2024 update. Environ Epigenet. 2024, 10(1): dvae004. DOI: https://doi.org/10.1093%2Feep%2Fdvae004
71. Wołowiec A, Wołowiec Ł, Grześk G, et al. The Role of Selected Epigenetic Pathways in Cardiovascular Diseases as a Potential Therapeutic Target. Int J Mol Sci. 2023, 24(18):13723. DOI: https://doi.org/10.3390%2Fijms241813723
72. Hu S, Chen L, Zeng T, Wang W, Yan Y, Qiu K, Xie Y, Liao Y. DNA methylation profiling reveals novel pathway implicated in cardiovascular diseases of diabetes. Front Endocrinol (Lausanne). 2023, 14:1108126. DOI: https://doi.org/10.3389/fendo.2023.1108126
73. Kassem NM, Abdelmegid YA, El-Sayed MK, Sayed RS, Abdel-Aalla MH, Kassem HA. Nutrigenomics and microbiome shaping the future of personalized medicine: a review article. J Genet Eng Biotechnol. 2023, 21(1):134. DOI: https://doi.org/10.1186%2Fs43141-023-00599-2
74. Unadkat SV, Padhi BK, Bhongir AV, Gandhi AP, Shamim MA, Dahiya N, Satapathy P, Rustagi S, Khatib MN, Gaidhane A, Zahiruddin QS, Sah R, Serhan HA. Association between homocysteine and coronary artery disease-trend over time and across the regions: a systematic review and meta-analysis. Egypt Heart J. 2024, 76(1):29. DOI: https://doi.org/10.1186/s43044-024-00460-y
75. Lioudyno VI, Tsymbalova EA, Chernyavskaya EA, Scripchenko EY, Bisaga GN, Dmitriev AV, Abdurasulova IN. Association of

Increased Homocysteine Levels with Impaired Folate Metabolism and Vitamin B Deficiency in Early-Onset Multiple Sclerosis. Biochemistry (Mosc). 2024, 89(3):562-573. DOI: https://doi.org/10.1134/s0006297924030143

76. Nappi F, Avtaar Singh SS, Jitendra V, Alzamil A, Schoell T. The Roles of microRNAs in the Cardiovascular System. Int J Mol Sci. 2023, 24(18):14277. DOI: https://doi.org/10.3390%2Fijms241814277
77. Montero O. Cholesterol in virus entry into host cell: diet, phytosterols and stains. Functional Foods in Health and Disease 2021, 11(3): 104-115. DOI: https://www.doi.org/10.31989/ffhd.v11i3.780
78. Liu Y, Deng J, Zhao T, Yang X, Zhang J, Yang H. Bioavailability and mechanisms of dietary polyphenols affected by non-thermal processing technology in fruits and vegetables. Curr Res Food Sci. 2024, 8:100715. DOI: https://doi.org/10.1016%2Fj.crfs.2024.100715
79. Godos J, Romano GL, Gozzo L, et al. Resveratrol and vascular health: evidence from clinical studies and mechanisms of actions related to its metabolites produced by gut microbiota. Front Pharmacol. 2024, 15:1368949. DOI: https://doi.org/10.3389%2Ffphar.2024.1368949
80. Aghababaei F, Hadidi M. Recent Advances in Potential Health Benefits of Quercetin. Pharmaceuticals (Basel). 2023, 16(7):1020. DOI: https://doi.org/10.3390%2Fph16071020
81. Mani A. Update in genetic and epigenetic causes of hypertension. Cell Mol Life Sci. 2024, 81(1):201. DOI: https://doi.org/10.1007%2Fs00018-024-05220-4
82. Mengozzi A, Costantino S, Mongelli A, et al. Epigenetic Signatures in Arterial Hypertension: Focus on the Microvasculature. Int J Mol Sci. 2023, 24(5):4854. DOI: https://doi.org/10.3390%2Fijms24054854
83. Karabaeva RZ, Vochshenkova TA, Mussin NM, Albayev RK, Kaliyev AA, Tamadon A. Epigenetics of hypertension as a risk factor for the development of coronary artery disease in type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2024, 15:1365738. DOI: https://doi.org/10.3389%2Ffendo.2024.1365738
84. Wu YL, Lin ZJ, Li CC, et al. Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. Signal Transduct Target Ther. 2023, 8(1):98. DOI: https://doi.org/10.1038%2Fs41392-023-01333-7
85. Suárez R, Chapela SP, Álvarez-Córdova L, et al. Epigenetics in Obesity and Diabetes Mellitus: New Insights. Nutrients. 2023, 15(4):811. DOI: https://doi.org/10.3390%2Fnu15040811
86. Kowluru RA, Mohammad G. Epigenetic modifications in diabetes. Metabolism. 2022, 126:154920. DOI: https://doi.org/10.1016%2Fj.metabol.2021.154920
87. Marino P, Mininni M, Deiana G, et al. Healthy Lifestyle and Cancer Risk: Modifiable Risk Factors to Prevent Cancer. Nutrients. 2024, 16(6):800. DOI: https://doi.org/10.3390%2Fnu16060800
88. Smith ENL, Chandanathil M, Millis RM. Epigenetic Mechanisms in Obesity: Broadening Our Understanding of the Disease. Cureus. 2023, 15(10):e47875. DOI: https://doi.org/10.7759%2Fcureus.47875
89. Fouziya S, Krietenstein N, Mir US, et al. Genome wide nucleosome landscape shapes 3D chromatin organization. Sci Adv. 2024, 10(23):eadn2955. DOI: https://doi.org/10.1126%2Fsciadv.adn2955
90. Sexton CL, Godwin JS, McIntosh MC, et al. Skeletal Muscle DNA Methylation and mRNA Responses to a Bout of Higher versus Lower Load Resistance Exercise in Previously Trained Men. Cells. 2023;12(2):263. DOI: https://doi.org/10.3390%2Fcells12020263
91. Urošević M, Nikolić L, Gajić I, Nikolić V, Dinić A, Miljković V. Curcumin: Biological Activities and Modern Pharmaceutical Forms. Antibiotics (Basel). 2022;11(2):135. DOI: https://doi.org/10.3390%2Fantibiotics11020135
92. Mondal S, Rathor R, Singh SN, Suryakumar G. miRNA and leptin signaling in metabolic diseases and at extreme environments. Pharmacol Res Perspect. 2024, 12(4): e1248. DOI: https://doi.org/10.1002/prp2.1248
93. Chen P, Wang Y, Chen F, Zhou B. Epigenetics in obesity: Mechanisms and advances in therapies based on natural products. Pharmacol Res Perspect. 2024, 12(1):e1171. DOI: https://doi.org/10.1002%2Fprp2.1171