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Nutrigenomics: linking food to genome

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REVIEW

Abstract

Nutrigenomics has an undoubtedly immeasurable potential for revamping human health. It has become an important regimen due to its consequential role in medical and nutritional sciences. It is an interdisciplinary science that amalgamates the information from physiology, pathology, genetics, molecular biology, and nutrition to establish the effects of ingested nutrients on expression and regulation of genes. The ultimate aim of nutrigenomics is to ascertain the nutritional requirement of an individual in accordance with genetic makeup. Moreover, it aims to purvey treatment in the management of certain ailments having a dietary role based on individual's genomic profile. Therefore, vast research in the field of nutritional genomics is a dire need to make people aware regarding their health and diet relationship. Here, we have given an overview of nutrigenomics coupled with novel technologies to produce utilitarian information for health professionals and researchers by divulging certain properties that interfere with the genomic machinery.

Keywords: gene; interaction; micronutrients; nutrigenomics; nutrition

Introduction

Although our connection with food is complicated and ever-evolving, our desire for it is fundamental (Grayson, 2010). Influence of diet and environment on the health of an organism is not a new concept (Emilien and Hollis, 2017). Nature alone cannot contribute to molecular mechanism that eventually governs the health of a human being (Mead, 2007). The exogenous environmental factors that also include dietary nutrients and the genetic makeup of an individual play an important role in expression of a phenotypic trait via the central dogma of biology (Reddy *et al*., 2017). Over the 20th century, nutritional scientists focused on the discovery, use, and administration of vitamins and minerals in order to treat the deficiency diseases such as scurvy in the case of vitamin C deficiency; colon cancer, heart disease, and immune dysfunction due to vitamin E deficiency; colon cancer, heart disease, and immune dysfunction due to folic acid deficiency; kwashiorkor and marasmus due to protein deficiency; nerve problem and memory loss due to deficiency of niacin (Dwivedi *et al.,* 2014; Mitra *et al*., 2005). Malnutrition has repeatedly been shown to be common among hospitalized patients in modern developed societies. We usually mention that in the developed countries such as the USA, UK, Spain, The Netherlands, and Canada, due to a wave of non-communicable diseases, there has been a shift from infectious disease predominance to communicable disease epidemic. So, the center of interest of nutritional science and modern medicine shifted to investigation on optimization and maintenance of homeostasis at all levels, namely, cellular, tissue, organ, and at whole body (Afshin *et al*., 2019; Mohan *et al*., 2007; Raj *et al*., 2007). This requires the basic understanding of the effect of nutrients at molecular level, involving nutrient-related interactions at the genome, proteome, and metabolome levels of individuals, which led to the shifting of nutrition research from

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physiology to molecular biology and genetics, giving rise to a new approach of nutrigenomics (Neeha and Kinth, 2013). Earlier, nutrigenomics was defined as "the effect of nutrients on the expression of an individual's genetic makeup" (Mead, 2007; Riscuta, 2016). Recently, the definition was broadened to understand the influence of nutrients on the genome, transcriptome, proteome, and metabolome (Ronteltap *et al*., 2009). It involves characterizing the gene products, their physiological functions, and interactions (Neeha and Kinth, 2013). It also analyzes the effects on gene expression due to the bioactive food components (nutrients and non-nutrients) (Alagawany *et al.,* 2022; Koziołkiewicz, 2011).

Bioactive food components act as dietary signals (Chadwick, 2004) and from a nutrigenomics point of view, cellular sensor systems such as peroxisome proliferated-activated receptor γ (PPARγ) and retinoid X receptors (RXRs) recognize these dietary signals which influences the expression of genes, synthesis of proteins, and production of metabolites (Amin *et al.,* 2012). Nutrigenomics seeks to understand how nutrition influences homeostasis due to these dietary signatures (Müller and Kersten, 2003). It also aims to understand the mechanisms that influence the genetic susceptibilities (van Ommen and Stierum, 2002) by identifying the genes that sway the risk of diseases related to diet on a genome-wide scale.

Origin of Nutrigenomics

With the advancement in science and technology, particularly after the completion of the human genome project, scientists appeared skeptical and started questioning like (1) Are gene expressions and metabolic responses the outcome of interaction between genotype and environment (including nutrient)? (2) Will metabolic processes sway the individual in response to gene expression? (3) How does nutrient–gene interaction lead to the prescription of exact diets (Cozzolino and Cominett, 2013)? To answer the above questions, a new subject in the form of nutrigenomics came into existence (Dauncey, 2012). The term "nutrigenomics" was first described by Peregrin (2001) and subsequently appeared in a review published in the journal Current Opinion in Biotechnology (van Ommen and Stierum, 2002). There are several problems with our health system. Firstly, we actually treat people after they get sick, neither do much to keep them healthy nor understand what's going on while they are healthy; and secondly, the one size fits all approach, that is, giving people the same treatment even though they are all individuals and may respond differently. Human genetics so far has largely focused on explicit genetic diseases with possible genetic basis. There have been extremely limited therapeutic benefits, apart from some diagnostic applications. Based on an individual's genetic makeup or genomic profile, development of new drugs would become the gold standard (Brand *et al*., 2021). A renowned biologist and director Professor Yvonne Dragon, Division of Systems Toxicology, believes that new biological understanding will come from familiarity of genes, proteins, and metabolites to fight common diseases (Kumar, 2007a).

Role of food in disease prevention and management

In recent years, food has become the central dogma for nutritionists in establishing interaction between lifestyle-associated metabolic diseases. Reconsideration of "food as medicine" by general public, scientific developments in health sector, and demand for disease-combating diet has opened new area for intervention in health-related issues, which allows individuals to improve their health and prevent diseases (Ohlhorst *et al.,* 2013). Dietary fibers have a protective effect against bowel cancer (Kelley *et al.,* 2007). Growth of colonic tumors in both in-vitro and in-vivo systems is inhibited by consumption of fish oil which is rich in omega-3 fatty acids (Syvertsen *et al.,* 2007). Fruits and vegetables rich in bioactive components can prevent carcinogenesis by several mechanisms such as blocking metabolic activation through increasing detoxification. Detoxification enzymes such as flavonoids, phenols, isothiocyanates, allyl sulfur compounds, indoles, and selenium can be modulated on consuming plant foods (Fuller, 1992; Mitall and Garg, 1992). Intake of proper diet with sufficient minerals and vitamins that are involved in regulatory and enzymatic processes reduces the risk of cancer. The deficiency of these micronutrients may lead to abnormalities. For example, zinc and folate are involved in DNA repairing process. Further natural compounds from plant source such as apigenin (celery, parsley), curcumin (turmeric), epigallocatechin-3-gallate (green tea), resveratrol (red grape, peanuts, and berries), genistein (soybean), and allyl sulfur (garlic) have been reported to affect the cell cycle by different mechanisms (Farouque *et al.,* 2006).

Personalized nutrition

Nutrigenomics contribute in the designing of optimized dietary intervention strategies to restore and improve metabolic homeostasis, improve health and wellbeing, and prevent diet-related diseases. However, personalized diets that could be uniquely tailored according to the specific demands of a given individual considering his/her genetic background, lifestyle, and history are also included here. The speed of penetration of this new science in daily life is expected to come from both the diversity and complexity of food and food practices and the

complexity of our metabolic systems. Our diet is omnivorous and consists of a variety of plants, animals and their derived products, water, as well as fungi, yeasts, and a diversity of bacteria. In the past, many food compounds were dismissed because no obvious nutritional roles were known for them. Most foods are a vastly complex and synergistic or non-synergistic mix of several nutrients and many other components, the importance of which is being unveiled step by step. We are exposed to these complex mixtures throughout life, and while our biochemical processes extract energy, building blocks, and regulators from food to enable us to grow and function properly they are, in addition, dependent on other factors, including physical activity, feeling and emotion, and social and economic factors (Palou, 2007).

Nutrigenomics and Related Terms

The nutrient requirements of different individuals differ due to considerable heterogeneity in the sequence of the human genome (Ramos-Lopez *et al*., 2017). Nutrigenetics explained this genetic difference as the key basis for diverse response to the diet among different individuals (Elsamanoudy *et al*., 2016; Farhud and Yeganeh, 2010). These differences may not be at whole gene level but rather can be at single nucleotide polymorphisms level (Irimie *et al*., 2019). Thus, both nutrigenetics and nutrigenomics are two sides of a same coin (Figure 1). It holds much promise for providing better nutritional advice by identifying the dietetic components having both detrimental and beneficial health effects. It also determines the necessity of individual nutritional requirement based on genetic makeup and understands the association between diet and chronic diseases (Sales *et al*., 2014). This can occur in three ways:

1. **Regulation of transcription factors and transcription process**

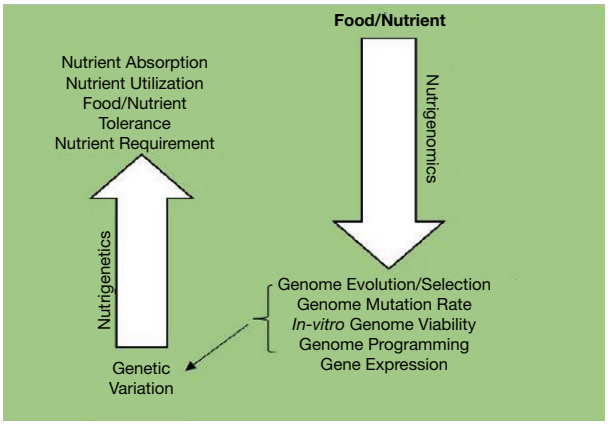

Figure 1. Mechanisms of influence of nutrients on gene expression.

Nutrients behave as transcription factors after interacting with a receptor, which binds tightly to DNA and intensely induces gene expression. For instance, as in the case of lac operon, which is by default turned off if lactose is not present in a cell (e.g., bacterial cell) (Siddique *et al*., 2009). The lacI inhibitor gene binds with promoter region and as a result will not allow RNA polymerase to transcribe, and hence no transcription of DNA takes place. However, if lactose is present in the medium, it will interact and change the structural conformation of lacI, thus losing its capacity to attach with the promoter. RNA polymerase easily binds with the promoter to transcribe the structural genes (lacY, lacA, lacZ) to produce proteins such as β-galactosidase, permease, and transacetylase, respectively. These proteins help in the uptake and breakdown of lactose to release energy.

2. **DNA susceptibility to transcriptional machinery and regulation of chromatin structure**

Nutrients can alter the structure of DNA by a process known as epigenetics (Park *et al.,* 2017). Epigenetics denotes continual DNA configurational changes without change in sequence that results in the alteration of expression of genetic material (Table 1).

The sustained effects of epigenetic mechanism are mediated by chromatin remodelling and methylation of DNA (Liu and Qian, 2011). A methyl group is added to cytosine base to repress gene activity, or tails of histones are attached with combination of different molecules that alters activity of the DNA wrapped around them and ultimately gene expression (DNA methylation) (Fuks, 2005). Similarly active chromatin, that is, non-methylated cytosine and acetylated histones indicate that gene is active and hence transcription is possible. On the other hand, silent chromatin, that is, methylated cytosine and non-acetylated histones indicate that gene is silent and hence transcription is inhibited. The folic acid–rich diet influences DNA methylation during folic acid metabolism and can switch off some important genes (Colson *et al*., 2017; Crider *et al*., 2012). Dolinoy *et al*. (2006) in an experiment reported the role of folate-rich diet in mother mouse, wherein methylated IAP sequences of the offspring genome and the silencing of agouti gene resulted in normal brown color of child coat, whereas, folate-deficient diet resulted in yellow coat color, obesity, and tumors.

3. **Prevention of DNA damage**

Cytokinesis-blocked lymphocyte (CBMNcyt) with micronucleus assay is commonly used with peripheral blood lymphocytes and is presently the best biomarker for nutritional genomic studies of DNA damage. The extent of chromosomal DNA damage is

Table 1. Key plants elements with epigenetic modifications.

Sl. No.	Key plants	Bioactive element	Epigenetic functions	Reference(s)
1.	Apples	Phloretin	Demethylation, reexpression TSGs, HDAC inhibition	Orlikova *et al*., 2012; Paluszczak *et al*., 2010
2.	Broccoli	Isothiocyanates	Chromatin remodeling, activation of p21 gene, induces DNA methylation and gene reactivation (cyclin D2)	Ho *et al*., 2009; Hsu *et al*., 2011; Myzak *et al*., 2004
3.	Cashew nuts	Anacardic acid	HATi, DNA repair	Balasubramanyam *et al*., 2003; Link *et al*., 2010
4.	Fenugreek	Rhaponticin	DNA repair and gene reactivation	Wani and Kumar 2016
5.	Citrus	Hesperidin	DNMT inhibitor	Fang *et al*., 2007
6.	Cinnamon	Coumaric acid	DNMT inhibitor, increases p53 acetylation	Olaharski *et al*., 2005; Stavinoha and Vattem 2015
7.	Coffee	Caffeic acid	DNMT inhibitor	Lee and Zhu 2006
8.	Garlic	Allyl mercaptan	Histone acetylation, HDAC inhibitor	Nian *et al*., 2008
9.	Grapes	Resveratrol	DNMT inhibitor, induces DNA demethylation and gene reactivation	Howitz *et al*., 2003; Paluszczak *et al*., 2010; Stefanska *et al*., 2010
10.	Soyabean	Genistein	DNMT inhibitor, decreases HDAC activities, increases acetylation at TSG	Bosviel *et al*., 2012; Fang *et al*., 2005; Majid *et al*., 2008
11.	Tea	Epigallocatechin gallate (EGCG)	DNMT inhibitor	Fang *et al*., 2003; Lee *et al*., 2005
12.	Tomatoes	Lycopene	Induces DNA demethylation and gene reactivation (GSTP1, RARbeta, HIN-1)	King-Batoon *et al*., 2008
13.	Red pepper	Capsaicin	DNMT inhibitor	Srinivasan 2013
14.	Turmeric	Curcumin	DNMT inhibitor	Marcu *et al*., 2006; Shu *et al*., 2011
15.	Ginger	Gingerol	Reduces platelet aggregation and LDL atherogenic modifications	Tchombe *et al*., 2012
16.	Mango, Blackberry	Gallic acid	HATi	Choi *et al*., 2009b
17.	Frequently found in fruits and vegetables	Quercetin	DNMTi, induces p16 promoter, demethylation and gene expression	Howitz *et al*., 2003; Tan *et al*., 2009
18.	Red cabbage, red onion	Cyaniding	DNMTi	Paluszczak *et al*., 2010
19.	Found in walnuts, many other fruits and vegetables	Myricetin	DNMTi	Fang *et al*., 2007; Lee *et al*., 2005; Paluszczak *et al*., 2010

measured by the occurrence of micronuclei in lymphocytes. The accumulation of micronuclei in the CBMNcyt assay is particularly sensitive to nutritional deficiency or excess. Mead (2007) reported the association of micronuclei with nutrition and noted in studies that even moderate folate deficiency within the physiological range in cultured lymphocytes caused as much DNA damage as 10 times the annual allowed limit of exposure to X-rays. Basically, micronuclei originate from chromosomes that fail to engage the spindle during nuclear division or from acentric chromosome fragments and act as biomarkers of chromosome loss or chromosome breakage, respectively. By using a cytokinesis-blocking agent (cytochalasin-B), once-divided cells that can express this damage are identified as binucleated cells. Within these binucleated cells, it is also possible to measure nucleoplasmic bridges, which arise from dicentric chromosomes and nuclear buds (NBUDs), a biomarker for gene amplification (Figures 2 and 3). Similarly, Fenech (2012) also reported that DNA damage can be caused due to deficiency or excess of nutrition and that the effects are of the same magnitude as that of many common environmental toxicants.

Diet-gene regulation/Nutrients and gene expression

Nutrigenomics illustrates the influence of nutrients on gene or protein expression that is regulated at specific time under particular environment and also generates response that results from simultaneous functioning of gene or protein networks in regulation of related human disease or disorder. In recent time, there is more interest in nutrigenomics research to understand the effects of nutritious food and medication on metabolic disorders

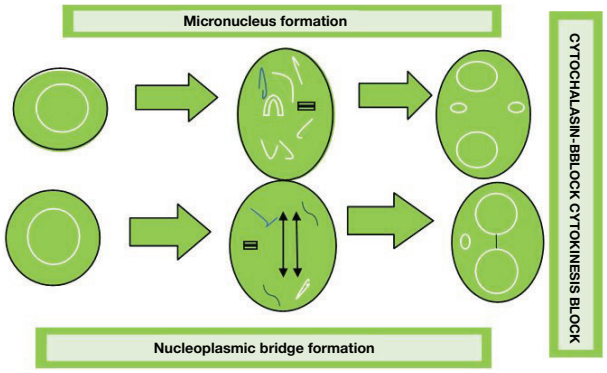

Figure 2. Expression of micronuclei and nucleoplasmic bridges during nuclear division.

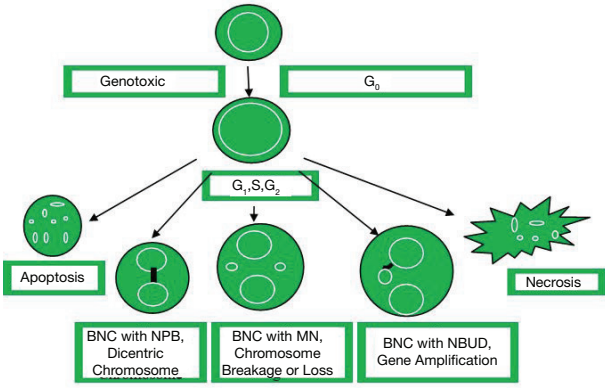

Figure 3. Biomarkers scored in the cytokinesis-block micronucleus cytome assay.

associated with lifestyle transition. Dietary interventions are supposed to play essential role in maintenance of an individual's well-being and immunity transformation.

Effect of carbohydrates on gene expression

The simplest monosaccharide (glucose) in nature provides a best model of how living organisms deal effectively by developing regulatory mechanisms with a varying level of nutrients supply (Lee *et al.*, 2008). Glucose is the primary physiological stimulus in the β-cells of pancreas for the regulation of insulin synthesis and secretion (Yamashita *et al.*, 2001). Furthermore, expression of genes encoding lipogenic and glycolytic enzymes, for example, acetyl-CoA carboxylase in liver is induced by glucose in presence of insulin (Henquin, 2000). Thus, it plays a key role in transcriptional regulation, though insulin and glucagon were long known as critical in regulating gene expression. (Sanhueza and Valenzuela, 2012). Unbalanced diets increase the risk of developing chronic diseases by altering nutrient–gene interactions (Fukasawa *et al.*, 2010). Diets rich in excess carbohydrates increase the expression of ChREBP (carbohydrate response element-binding protein), which regulates lipid and glucose metabolism at the transcription level, thereby contributing to the development of metabolic diseases (Lizuka, 2017). The ChREBP plays a significant role in glucose intolerance, fatty liver, and dyslipidemia in humans (Benhamed *et al.*, 2012).

Effect of lipids on gene expression

Profound effects of fat on gene expression led to alteration in growth, differentiation of cells, and metabolism. Lipids activate various transcription factors such as PPARs, SREBP-1, LXRs, HNF4, and FXR (Table 2) responsible for lipogenesis, glucose metabolism, and so on. (Georgiadi and Kersten, 2012). However, PPAR (peroxisome proliferator–activated receptor), an important transcriptional factor that is copiously expressed in enterocytes, mediates the effects of dietary lipids on gene expression (Bordoni *et al.*, 2021).

Besides regulating various functions such as intestinal nutrient transport and metabolism, intestinal cholesterol flux, intestinal motility, and lessening oxidative stress, PPAR acts as a master regulator of fatty acid catabolism. So, PPAR is therapeutically important for patients suffering from inflammatory bowel disease (Reen *et al.*, 2015). The nutritional effect of these fatty acids verily depends on the level of saturation. The ω-3 polyunsaturated fatty acids as anti-inflammatory agents interact with genes involved in cancer and various inflammations, hence proving their role in nutrigenetics (Deckelbaum *et al.*, 2006). They also have a significant effect on cardiac arrhythmia (Brouwer *et al.*, 2002). Similarly, oleic and linoleic fatty acids decrease plasma levels of low-density lipoprotein and cholesterol (Sacks and Katan, 2002).

Effect of proteins on gene expression

Protein kinase C (PKC), calcium ion (Ca^{2+}), and K^+ channel proteins influence the normal level of insulin secretion by increasing ATP to ADP ratio through glucose metabolism and closes K^+ ATP channel, leading to depolarization of β-cells (Szymczak-Pajor and Sliwinska, 2019). Fekete and Brown (2007) reported that protein-rich diets result in the moderation of total body fat by causing a shortage of mRNA which is essential for fatty acid synthase gene expression in the adipocytes. Similarly, a low input of essential amino acids triggers reduction in synthesis and also alters the functions of norepinephrine and cAMP by means of a protein called CHOP (or C/EBP, also known as a stress-responsive transcription factor) (Zhang *et al.*, 2002). It attaches with

Table 2. Transcription-factor pathways mediating nutrient–gene interactions.

Nutrients	Compounds	Transcription factors	Reference(s)
Carbohydrates	Glucose	USFs, SREBPs, ChREBP	Müller and Kersten 2003; Uyeda *et al*., 2002
Fats	Cholesterol	PPARs, SREBPs, LXRs, HNF4, FXR	Müller and Kersten 2003; Edwards *et al*., 2000; Horton *et al*., 2002
Proteins	Amino acids	C/EBPs	Geiger *et al*., 2016
Micronutrients:			
Vitamins	Vitamin A	RAR, RXR	Müller and Kersten, 2003; Rahman *et al*., 2020; Anitha *et al*., 2021
	Vitamin D	VDR	
	Vitamin K	PXR	
	Calcium	Calcineurin/NF-ATs	Schuster 2006; Rahman *et al*., 2020
Minerals	Iron	IRP1, IRP2	
	Zinc	MTF1	
Other food compounds	Flavonoids	ER, NFκB, AP1 ER, NFκB, AP1 ER, NFκB, AP1	Schuster 2006; Baldwin 2019
	Xenobiotics	CAR, PXR	

AP1, activating protein1; CAR, constitutively active receptor; C/EBP-CAAT, enhancer binding protein; ChREBP, carbohydrate-responsive element-binding protein; ER, estrogen receptor; FXR, farnesoid X receptor; HNF, hepatocyte nuclear factor; IRP, iron regulatory protein; LXR, liver X receptor; MTF1, metal-responsive transcription factor 1; NFκB, nuclear factor κB; NFAT, nuclear factor of activated T cells; PPAR, peroxisome proliferated-activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; SREBP, sterol-responsive element-binding protein; USF, upstream stimulatory factor; VDR, vitamin D receptor.

gene expression enhancers and gets activated by means of stressful stimuli such as DNA damage, cellular growth arrest, and hypoxia (Ren *et al*., 2017).

Effect of micronutrients on gene expression

Micronutrients play a vital role in maintaining genome stability (Table 3) by regulating DNA synthesis, methylation, and repair (Fenech, 2012). Savini *et al.* (2016) and Surendran *et al.* (2018) communicated that identification of indispensable micronutrient-rich foods for DNA replication and repair or for the prevention of genome-damaging events is vital for maintaining proper health and metabolism in individuals. The amount of micronutrients that appear to be protective against genome damage varies greatly between foods (Fenech, 2005, 2008), as well as between individuals, due to taste preferences (Diószegi *et al*., 2019; Garcia-Bailo *et al*., 2009) or cultural or religious constraints (El-Sohemy *et al.,* 2007). Therefore, careful choices are need of the hour to formulate patterns of diet that are optimum for maintenance of genome health.

Tools of Nutrigenomics

New opportunities in the field of science are now possible with the discovery of various "omics" technologies discussed below, to aid in our understanding of the role and impact of various nutrients (nutrition) on individual's health.

1. Transcriptomics

The study of expression of genes at the mRNA level is known as transcriptomics. There are several methods to contour gene expression, however, DNA micro array is the most popular one. DNA microarray technology has successfully measured the changes in genetic expression by evaluating the interactions between diet and genes. In this technique, mRNA transcripts extracted from tissues are subjected to create complementary labeled strand of DNA (cDNA) through Reverse Transcriptase-*In Vitro* Transcription (RT-IVT). The labeled cDNA is hybridized with a probe (complimentary strand) speckled on a glass or nylon substrate (array) containing a set of genes of known sequences. Confocal fluorescent scanner is used to quantify the color intensity, and by examining the resulting image, raw data on gene expression is extracted. Using specific software, raw data is analyzed to determine up- and downregulation of genes with respect to control (Figure 4). Data obtained from microarray can be used by an investigator to establish which genes are expressed differently, that too at mRNA level and thus may be able to design better treatment strategies (Reecy *et al*., 2006). In comparison to the microarray technology, RNA sequencing technology (RNA-Seq), a novel transcriptomics method has proven tremendous analytical capability for gene expression studies. RNA sequencing technology holds great potential for studying nutrient–gene interactions and provides a comprehensive understanding of RNA expression at

Table 3. Role of micronutrients in maintaining genomic stability.

Sl. No.	Micronutrients	Role in genomic stability	Consequences of deficiency	Food uptake for remediation	Reference(s)
1.	Vitamin C and E	Prevention of DNA and lipid oxidation	Breaking of DNA strands, oxidative DNA lesions and lipid peroxide adducts on DNA	Tomato, brussels sprout, Drumstick leaves, kale, chilli, coriander leaves	Krajcovicová-Kudlácková *et al.*, 2006; Sorensen *et al.*, 2001
2.	Vitamin D	Antioxidant activity by increasing the level of glutathione in normal cells, induction of apoptosis in cancerous cells	Breaking of DNA strands, chromosome breaks and oxidative DNA lesions	Green vegetables, onion, chow chow	Schafer and Cockfield 2019; Pizzino *et al.*, 2017
3.	Folate and Vitamins B2, B6 and B12	Methylation of DNA, synthesis of dTMP	Uracil misincorporation in DNA and DNA hypomethylation	Beet root, potato, pepper, turnip, mushroom, garlic, cauliflower	Thomas and Fenech, 2009
4.	Vitamin B3 (Niacin)	Required as substrate for poly (ADP-ribose) polymerase, which is required for cleavage and rejoining of DNA and telomere	Impairment of DNA repair, chromosome breaks, mutagen sensitivity	Carrot, turnip, celery, mushroom, beans	Halliday *et al.*, 2010
5.	Zinc	Required as cofactor for Cu/ Zn superoxide dismutase, DNA replication, Zn finger proteins	Increased DNA damage and chromosomal breakage.	Spinach, broccoli	Lewis *et al.*, 2005; Yan *et al.*, 2008
6.	Iron	Required as component of ribonucleotide reductase and mitochondrial cytochromes	Reduced DNA repair, increased tendency for oxidative damage to mitochondrial DNA	Amaranthus, spinach, cabbage, carrot, beans	Zhang, 2014; Canniatti-Brazaca and Germano, 2011
7.	Magnesium	Cofactor for various DNA polymerases, required in nucleotide excision repair, essential for microtubule polymerization	Reduced fidelity of DNA replication, DNA repair and chromosomal segregation, survival of genomically aberrant cells	Green leafy vegetables	Hartwig, 2001
8.	Calcium	Plays an important role in chromosome segregation, apoptosis	Reduced DNA replication and repair, survival of aberrant cells	Agathi, curry leaves	Henneke *et al.*, 2017

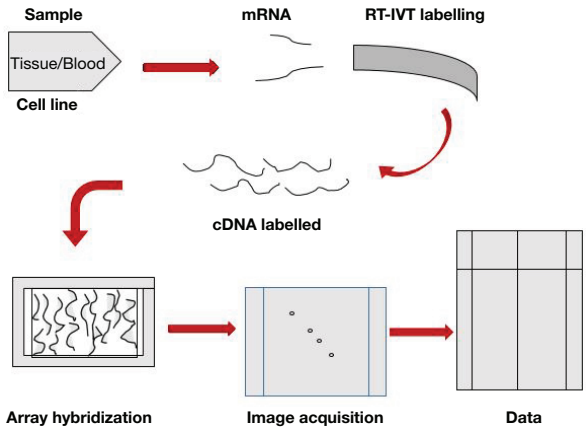

Figure 4. Schematic representation of micro array technology.

intracellular level in response to dietary interventions (Hasan *et al.*, 2019). The RNA sequencing technique or workflow can be described in three main steps: tissue examination in the lab, bioinformatics analysis of sequence data, and biological interpretation of bioinformatics data. This huge data gathering has a significant advantage in terms of speeding up our knowledge acquisition, which aids nutritionists in harnessing the molecular mechanisms of nutrition to improve production efficiency (Wang *et al.*, 2017)

2. Proteomics

Proteome refers to the total set of proteins expressed in a given cell. Proteomics studies are related to expression levels, structure of proteins, and biochemical activity. Thus, it addresses the questions of nutritional bioefficacy and identifies as well as quantifies bioactive proteins and peptides. In addition to techniques such as western blot, enzyme-linked immunosorbent assay (ELISA), immune histochemical staining, and mass spectrometry, it also uses protein-specific biomarkers for rapid disease diagnoses (Klopfleisch *et al.*, 2010). However, major platforms for proteomic studies of biomedical topics are ELISA and MS-based protein assays. Nowadays, MALDI-TOF or TOF-MS is an emerging technology for reliable and rapid diagnosis and microbial identification. Microbiologists have reported using MALDI-TOF

MS for a variety of purposes, including detection of antibiotic resistance, biological warfare agents, and blood and urinary tract pathogens, and in epidemiological studies (Weng *et al.,* 2021).

3. **Metabolomics**

The study which involves chemical processes in the metabolites is called metabolomics. Various techniques including nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectrometry (GC-MS), and high performance liquid chromatography (HPLC) analyze the whole metabolism. These techniques also reflect the behavior of different patterns of genes to contribute to the knowledge of how food containing over or under nutrients or secondary metabolites, which can affect the health or illness of an individual (Nielsen and El-Sohemy, 2012). Predominantly the two methods, namely, NMR and mass spectrometry are used for conducting metabolic studies to identify, quantify, display, and generate profiles of a number of metabolites with more robustness and sensitivity in a body fluid sample. The profiles are then run through monitors to generate data for interpretation (Kumar, 2007b).

Potential Issues Associated with Delivering Nutrigenomics

Nutrigenomics offers important health benefits for individuals; however, it raises certain legal, ethical, and social issues mainly with respect to nutritional and lifestyle advice as well as how public may access nutrigenetic tests, as discussed below.

Genetic tests and managing nutrigenomics information

Nutrigenomics approach like other genome-based science requires personal genetic information (Vineis and Christiani, 2004). Due to the personal nature of genetic information, it is important that the autonomy of a person regarding the decisions based on the information have to be respected (Horne and Vohl, 2020). This indicates that the information provided for testing purposes or research must be given without any fear or manipulation (Stevenson, 1999). Consent to genetic testing is usually linked with prospects of privacy, which involve liberty from unnecessary tests, and the ability to withhold information from third parties, namely, bio banks and electronic repositories, particularly in which samples are stored (Anonymous, 2006). As per professional obligations, the genetic information is expected to remain a top secret between patients and healthcare professionals (Joffe and Herholdt, 2020).

Genetic and nutritional counseling or delivering nutrigenomics services

Major barriers in offering nutrigenomics services to the public include lack of proper education in nutrition, genetics, and practitioners (Hudson *et al.*, 2007). Most practitioners in the healthcare sector do not have enough expertise in molecular testing and clinical genetics as well as lack sufficient knowledge in nutritional science, which is required to infer nutrigenomics tests (Murray adn Botkin, 1995; Roosan *et al*., 2022). It is mostly true for physicians, who are usually hesitant to provide advice in nutrition-related matters to patients due to lack of sufficient confidence in their nutrition knowledge (Kolasa, 2005). Therefore, practitioners must know how to understand and communicate sensitive information during counseling to patients on nutrigenomics (Kurzenhauser and Hertwig, 2006). Besides, sufficient knowledge about nutrition is required to advice patients about modification in their diets as well as how to quantify risk, to design test outcomes, and to deal with false negative or positive test results (Marteau, 1999), as these are highly susceptible to false impression, even by healthcare professionals.

Nutrigenomics Products

Nutrigenomics encourages different perspective on foods, healthy, quick to consume and digest, and easy to carry (Ashwell, 2004). According to this, the nutrigenomics tools contribute to the search for novel, functional, bioactive compounds intended to have effects like drugs, but without being categorized as drugs (Kruger and Mann, 2003).

Functional foods

These are very important groups of food having some important bioactive ingredients linked with growth, development, and prevention from diseases (Utkina and Karagodin, 2021). See Table 4. In Japan, nearly 350 food items have been accepted as functional, with each having specified health claims such as for high cholesterol, hypertension, diabetes, and hypotension (Htun *et al*., 2017). The trends in the development of functional foods include certain minerals, vitamins, and antioxidants with reduced calorie content, lower fat content or with healthier fat content as well as having low glycemic index (Garcia-Casal, 2007). Phytosterols, phytoestrogens, fructo-oligosaccarides, omega-3 fatty acids, and polyphenols are among others (Nijveldt *et al*., 2001). Because the inception of agriculture and livestock, genetics has been applied in food for improving the edible plant's genome. Either due to no load or less pesticides, these are considered as healthier and safer (Alavanja *et al*., 2004). Some

Table 4. Transgenic crops approved for commercial use.

Sl. No.	Products	Altered trait	Company	Year	Trade name
1.	Tomato	Thicker skin and altered pectin content	Zeneca/Petoseed	1995	-
2.	Potato	*AmA1*gene (improved protein content)	Monsanto Company	2010	Protato
3.	Squash	Resistant to viruses	Ashgrow seeds	1995	Freedom II
4.	Rape seed	Altered fatty acid composition	Calgene Inc.	1995	Laurical
5.	Papaya	Resistant to viruses	Cornell University	1997	-
6.	Corn	*Bt Cry* protein	Monsanto Company	1996	Yieldgard
7.	Cauliflower	Introgression of '*Or*' gene (β-carotene rich)	Cornell University	-	-
8.	Soybean	Resistant to weedicide	Monsanto Company	1995	Roundup ready

Table 5. Reported sanative effects of foods in different diseases.

Sl. No.	Foods	Diseases	References
1.	Garlic, ginger, turmeric cloves	Cardiovascular and bone diseases	Rastogi *et al*., 2017
2.	White brinjal, fenugreek, pomegranate	Type 2 diabetes	Khan *et al*., 2009
3.	Saffron, turmeric, basil	Obesity	Alappat *et al*., 2010
4.	Onion, mint, garlic, fenugreek	Neurodegenerative diseases and protection against oxidative damage to red blood cells	Hwang *et al*., 2009; Kaviarasan *et al*., 2004
5.	Cardamom, cinnamon	Hypertension	Davis and Yokoyama, 2011
6.	Black pepper, bay leaf	Gastrointestinal diseases	Speroni *et al*., 2011
7.	Mustard	Bladder cancer	Bhattacharya *et al*., 2010

organizations (environmental) still accuse that these foods act as poison for one's health and as well as for the environment. However, so far there is no scientific evidence indicating any risks to the health of consumers (Vidal, 2009).

Transgenic foods

Throughout the world, several transgenic foods have been commercialized (Table 5), mostly in Australia, China, the United States of America, and Canada. The known ones are Bt corn, having endotoxin derived from *Bacillus thuringiensis*, which kills the larvae of stem borer insects and soybeans resistant to herbicide glyphosate (Broderick *et al*., 2006).

Nutraceuticals

Nutraceuticals comprising "any nontoxic food extract supplement that has scientifically proven health benefits for both disease treatment and prevention" (DeFelice, 1995) provide protection against disorders, for example, cancer, obesity, high blood pressure, cardiovascular diseases (CVDs), gastrointestinal tract disorder, type II diabetes, inflammation, microbial, viral, and parasitic infections, psychotic diseases, spasmodic disorders, and ulcers. (Abbasi *et al*., 2015).

Dietary supplements

Diet is an important factor in cancer etiology and prevention. Ayurvedic medicine prescribes many plant-based medicines for the treatment of cancer. Turmeric has shown to be a potent antioxidant and anti-inflammatory agent, with additional promise as a chemo-preventive agent. Many chronic diseases are polygenic and result from interaction between genes and environmental factors. Dietary intervention based on nutritional requirement, nutritional status, and genotype (i.e., "individualized nutrition") can be used for the prevention, control, or treatment of chronic diseases such as CVDs, metabolic syndromes, and cancer (Afman and Müller, 2006). These disorders are partly mediated by chronic exposure to certain food components. For example, the association between the amount of calories (Jenkins *et al*., 1998), the levels and types of vitamins, fat, and carbohydrates with atherosclerosis, diabetes, obesity, cancer, hypertension, and other chronic diseases has been demonstrated (Kumar, 2007a).

HCA-SX or Super Citrimax, a novel derivative of HCA (dried fruit rind of *Garcinia cambogia*, also known as Malabar tamarind), is a unique source of (–)-hydroxycitric acid (HCA). It is safe when taken orally and is bioavailable in the human plasma. Under the experimental conditions, Roy *et al.* (2004) demonstrated that HCA-SX supplement has been observed to be conditionally effective

in weight management and lowered abdominal fat leptin expression in experimental animals as well as in humans. In 2008, Lau et al. showed that supplementation of HCA and niacin-bound chromium (III) is safe and efficacious for weight loss.

Conclusions and Future Perspectives

The accurate and specific knowledge of dietary requirements might be useful to mitigate or prevent chronic diseases and also helps to understand the influence of nutrition on homeostasis, metabolic pathways and develop dietary-interventional strategies. Nutrigenomics laid the foundation for understanding variability in preferences, requirements, and responses to diet by humans. It acts as a new tool for nutritional research by targeting the specific gene through nutritional manipulation to alleviate the problems or to get desired performance associated with health and production. This approach would provide long- and short-term benefits to individual's health by initiating the diet-specific new diagnostic tests against the unfavorable responses to diet, by identification of specific populations with specific nutrient requirements. In future, scientists will constantly contribute to develop new innovations in nutrigenomics research, which will certainly update our basic understanding of nutrient–gene relationship with the help of molecular technologies, especially next generation sequencing. Therefore, future researches should focus on nutrient–gene relationship for nutritional therapy at personal level.

References

Abbasi, A.M., Shah M.H. and Khan M.A., 2015. "Phytochemicals and Nutraceuticals," in wild edible veetables of lesser Himalayas. Cham: Springer. pp. 31–65. https://doi.org/10.1007/978-3-319-09543-1_3

Afman, L. and Müller, M., 2006. Nutrigenomics: from molecular nutrition to prevention of disease. Journal of the American Dietetic Association. 106(4):569–576. https://doi.org/10.1016/j.jada.2006.01.001

Afshin, A., Sur, P.J., Fay, K.A., Cornaby, L., Ferrara, G., Salama J.S., et al., 2019. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 393(10184): 1958–1972.

Alagawany, M., Elnesr, S.S., Farag, M.R., El-Naggar, K. and Madkour, M., 2022. Nutrigenomics and nutrigenetics in poultry nutrition: an updated review. Worlds Poultry Science Journal. 78(2): 377–396. https://doi.org/10.1080/00439339.2022.2014288

Alappat, L. and Awad, A.B., 2010. Curcumin and obesity: evidence and mechanisms. Nutrition Reviews. 68:729–738. https://doi.org/10.1111/j.1753-4887.2010.00341.x

Alavanja, M., Hoppin, J. and Kamel, F., 2004. Health effects of chronic pesticide exposure: cancer and neurotoxicity. Annual Review of Public Health. 25: 155–197. https://doi.org/10.1146/annurev.publhealth.25.101802.123020

Amin, T., Mahapatra, H., Bhat, S.V. and Gulleria, S.P.S., 2012. Application of nutrigenomics in food industry: a review. Indian Journal of Horticulture. 2(3–4): 54–59.

Anitha, A., Viswambharan, V., Thanseem, I., Iype, M., Parakkal, R., Surendran, S.P., et al., 2021. Vitamins and cognition: a nutrigenomics perspective. Current Nutrition and Food Science. 17(4): 348–336. https://doi.org/10.2174/1573401316999200901180443

Anonymous, 2006. United States Government accountability office nutrigenetic testing: tests purchased from four websites mislead consumers. Washington: US GAO. pp. 1–27.

Ashwell, M., 2004. Concepts on functional food. Washington, DC: International Life Science Institute (ILSI), ILSI Press. 48 p.

Balasubramanyam, K., Swaminathan, V., Ranganathan, A. and Kundu, T.K., 2003. Small molecule modulators of histone acetyltransferase p300. Journal of Biological Chemistry. 278(21): 19134–19140. https://doi.org/10.1074/jbc.M301580200

Baldwin, W.S., 2019. Phase 0 of the xenobiotic response: nuclear receptors and other transcription factors as a first step in protection from xenobiotics. Nuclear Receptor Research. 6: 101447. https://doi.org/10.32527/2019/101447

Benhamed, F., Denechaud, P.D., Lemoine, M., Robichon, C., Moldes, M., Bertrand-Michel, J., et al., 2012.The lipogenic transcription factor ChREBP dissociates hepatic steatosis from insulin resistance in mice and humans. Journal of Clinical Investigation. 122(6): 2176–2194. https://doi.org/10.1172/JCI41636

Bhattacharya, A., Li, Y., Wade, K.L., Paonessa, J.D., Fahey, J.W. and Zhang, Y., 2010. Allyl isothiocyanate rich mustard seed powder inhibits bladder cancer growth and muscle invasion. Carcinogenesis. 31(12): 2105–2110. https://doi.org/10.1093/carcin/bgq202

Bordoni, L., Petracci, I., Zhao, F., Min, W., Pierella, E., Assmann, T.S., et al., 2021. Nutrigenomics of dietary lipids. Antioxidants. 10(7): 994. https://doi.org/10.3390/antiox10070994

Bosviel, R., Dumollard, E., Déchelotte, P., Bignon, Y.J. and Bernard-Gallon, D., 2012. Can soy phytoestrogens decrease DNA methylation in BRCA1 and BRCA2 oncosuppressorgenes in breast cancer? OMICS. 16(5): 235–244. https://doi.org/10.1089/omi.2011.0105

Brand, A., Evangelatos, N. and Özdemir, V., 2021. Placebogenomics: a new concept and tool for personalized medicine and public health. OMICS. 25(2): 76–78. https://doi.org/10.1089/omi.2020.0221

Broderick, N., Raffa, K.F. and Handelsman, J., 2006. Midgut bacteria required for *Bacillus thuringiensis* insecticidal activity. Proceedings of the National Academy of Sciences. 103(41): 15196–15199. https://doi.org/10.1073/pnas.0604865103

Brouwer, I.A., Zock, P.L., van Amelsvoort, L.G.P.M., Katan, M.B. and Schouten, E.G., 2002. Association between n-3 fatty acid status in blood and electrocardiographic predictors of arrhythmia risk in healthy volunteers. American Journal of Cardiology. 89(5): 629–631. https://doi.org/10.1016/S0002-9149(01)02314-1

Canniatti-Brazaca, S.G. and Germano, O.M.A., 2011. Iron availability in the presence of β-carotene in different mixtures. Food Science and Technology. 31(2): 327–333. https://doi.org/10.1590/S0101-20612011000200008

Chadwick, R., 2004. Nutrigenomics, individualism and public health. Proceedings of the Nutrition Society. 63(1): 161–166. https://doi.org/10.1079/PNS2003329

Colson, N.J., Naug, H.L., Nikbakht, E., Zhang, P. and McCormack, J., 2017. The impact of MTHFR 677 C/T genotypes on folate status markers: a meta-analysis of folic acid intervention studies. European Journal of Nutrition. 56(1): 247–260. https://doi.org/10.1007/s00394-015-1076-x

Cozzolino, S.M.F. and Cominetti, C., 2013. Biochemical and physiological bases of nutrition in different stages of life in health and disease. 1st ed. Sao Paulo, Brazil: Monole. Pp. 1257.

Crider, K.S., Yang, T.P., Berry, R.J. and Bailey, L.B., 2012. Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate's role. Advances in Nutrition. 3(1): 21–38. https://doi.org/10.3945/an.111.000992

Dauncey, M.J., 2012. Recent advances in nutrition, genes and brain health. Proceedings of the Nutrition Society. 71(4): 581–591. https://doi.org/10.1017/S0029665112000237

Davis, P.A. and Yokoyama, W., 2011. Cinnamon intake lowers fasting blood glucose: meta-analysis. Journal of Medicinal Food. 14: 884–889. https://doi.org/10.1089/jmf.2010.0180

Deckelbaum, R.J., Worgall, T.S. and Seo, T., 2006. n-3 fatty acids and gene expression. The American Journal of Clinical Nutrition. 83(6 Suppl): 1520S–1525S. https://doi.org/10.1093/ajcn/83.6.1520S

DeFelice, S.L., 1995. The Nutraceutical Revolution: its impact on food industry R&D. Trends in Food Science and Technology. 6(2): 59–61. https://doi.org/10.1016/S0924-2244(00)88944-X

Diószegi, J., Llanaj, E. and Adany, R., 2019. Genetic background of taste perception, taste preferences, and its nutritional implications: a systematic review. Frontiers in Genetics. 10: 1272. https://doi.org/10.3389/fgene.2019.01272

Dolinoy, D.C., Weidman, J.R., Waterland, R.A. and Jirtle, R.L., 2006. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environmental Health Perspectives. 114(4): 567–572. https://doi.org/10.1289/ehp.8700

Dwivedi, S., Shukla, S. and Goel, A., 2014. Nutrigenomics in breast cancer. In: Barh D., editor. Omics approaches in breast cancer. New Delhi: Springer. pp. 127–151. https://doi.org/10.1007/978-81-322-0843-3_6

Edwards, P.A., Tabor, D., Kast, H.R. and Venkateswaran, A., 2000. Regulation of gene expression by SREBP and SCAP. Biochimica et Biophysica Acta. 1529(1–3): 103–113. https://doi.org/10.1016/S1388-1981(00)00140-2

Elsamanoudy, A.Z., Neamat-Allah, M.A.M., Mohammad, F.A.H., Hassanien, M. and Nada, H.A., 2016. The role of nutrition related genes and nutrigenetics in understanding the pathogenesis of cancer. Journal of Microscopy and Ultrastructure. 4(3): 115–122. https://doi.org/10.1016/j.jmau.2016.02.002

El-Sohemy, A., Stewart, L., Khataan, N., Fontaine-Bisson, B., Kwong, P., Ozsungur, S., et al., 2007. Nutrigenomics of taste: impact on food preferences and food production. Forum of Nutrition. 60: 176–182. https://doi.org/10.1159/000107194

Emilien, C. and Hollis, J.H., 2017. A brief review of salient factors influencing adult eating behaviour. Nutrition Research Reviews. 30(2): 233–246. https://doi.org/10.1017/S0954422417000099

Fang, M., Chen, D., Yang, C.S., 2007. Dietary polyphenols may affect DNA methylation. Journal of Nutrition. 137(1 Suppl): 223S–228S. https://doi.org/10.1093/jn/137.1.223S

Fang, M.Z., Chen, D., Sun, Y., Jin, Z., Christman, J.K. and Yang, C.S., 2005. Reversal of hyper methylation and reactivation of p16INK4a, RARbeta, and MGMT genes by genistein and other isoflavones from soy. Clinical Cancer Research. 11(19 Pt 1): 7033–7041. https://doi.org/10.1158/1078-0432.CCR-05-0406

Fang, M.Z., Wang, Y., Ai, N., Hou, Z., Sun, Y., Lu, H., et al., 2003. Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Cancer Research. 63(22): 7563–7570.

Farhud, D.D. and Yeganeh, M.Z., 2010. Nutrigenomics and nutrigenetics. Iranian Journal of Public Health. 39(4): 1–14.

Farouque, H.M., Leung, M., Hope, S.A., Baldi, M., Schechter, C., Cameron, J.D., et al., 2006. Acute and chronic effects of flavanol-rich cocoa on vascular function in subjects with coronary artery disease: a randomized double-blind placebo controlled study. Clinical Science (London, England). 111(1): 71–80. https://doi.org/10.1042/CS20060048

Fekete, S. and Brown, D.L., 2007. Veterinary aspects and perspectives of nutrigenomics: a critical review. Acta Veterinaria Hungarica. 55(2): 229–239. https://doi.org/10.1556/avet.55.2007.2.9

Fenech, M., 2005. The Genome Health Clinic and Genome Health Nutrigenomics concepts: diagnosis and nutritional treatment of genome and epigenome damage on an individual basis. Mutagenesis. 20(4): 255–269. https://doi.org/10.1093/mutage/gei040

Fenech, M., 2008. Genome health nutrigenomics and nutrigenetics-diagnosis and nutritional treatment of genome damage on an individual basis. Food and Chemical Toxicology. 46(4): 1365–1370. https://doi.org/10.1016/j.fct.2007.06.035

Fenech, M., 2012. Folate (vitamin B9) and vitamin B12 and their function in the maintenance of nuclear and mitochondrial genome integrity. Mutation Research. 733(1–2): 21–33. https://doi.org/10.1016/j.mrfmmm.2011.11.003

Fukasawa, M., Ge, Q., Wynn, R.M., Ishii, S. and Uyeda, K., 2010. Coordinate regulation/localization of the carbohydrate responsive binding protein (ChREBP) by two nuclear export signal sites: discovery of a new leucine-rich nuclear export signal site. Biochemical and Biophysical Research Communications. 391(2): 1166–1169. https://doi.org/10.1016/j.bbrc.2009.11.115

Fuks, F., 2005. DNA methylation and histone modifications: teaming up to silence genes. Current Opinion in Genetics and Development. 15(5): 490–495. https://doi.org/10.1016/j.gde.2005.08.002

Fuller, R., 1992. History and development of probiotics. In: Fuller, R., (ed.,). Probiotics: the scientific basis. London, NY: Chapman & Hall. pp. 1–8. https://doi.org/10.1007/978-94-011-2364-8_1

Garcia-Bailo, B., Toguri, C., Eny, K.M. and El-Sohem, A., 2009. Genetic variation in taste and its influence on food selection. OMICS. 13(1): 69–80. https://doi.org/10.1089/omi.2008.0031

Garcia-Casal, M.N., 2007. The diet of the future: new technologies and their importance in the nutrition of the population. Venezuelan Annals of Nutrition. 20(2): 108–114.

Geiger, R., Rieckmann, J.C., Wolf, T., Basso, C., Feng, Y., Fuhrer, T., et al., 2016. L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. Cell. 167(3): 829–842. https://doi.org/10.1016/j.cell.2016.09.031

Georgiadi, A. and Kersten, S., 2012. Mechanisms of gene regulation by fatty acids. Advances in Nutrition. 3(2): 127–134. https://doi.org/10.3945/an.111.001602

Grayson, M., 2010. Nutrigenomics. Nature. 468(7327): S1. https://doi.org/10.1038/468S1a

Halliday, G.M., Surjana, D. and Damian, D.L., 2010. Role of nicotinamide in DNA damage, mutagenesis, and DNA repair. Journal of Nucleic Acids. 2010: 157591. https://doi.org/10.4061/2010/157591

Hartwig, A., 2001. Role of magnesium in genomic stability. Mutation Research. 475(1–2): 113–121. https://doi.org/10.1016/S0027-5107(01)00074-4

Hasan, M.S., Feugang, J.M. and Liao, S.F., 2019. A nutrigenomics approach using RNA sequencing technology to study nutrient–gene interactions in agricultural animals. Current Developments in Nutrition. 3(8): nzz082. https://doi.org/10.1093/cdn/nzz082

Henneke, G., Ralec, C., Henry, E., Lemor, M. and Killelea, T., 2017. Calcium-driven DNA synthesis by a high-fidelity DNA polymerase. Nucleic Acids Research. 45(21): 12425–12440. https://doi.org/10.1093/nar/gkx927

Henquin, J.C., 2000. Triggering and amplifying pathways of regulation of insulin secretion by glucose. Diabetes. 49(11): 1751–1760. https://doi.org/10.2337/diabetes.49.11.1751

Ho, E., Clarke, J.D. and Dashwood, R.H., 2009. Dietary sulforaphane, a histone deacetylase inhibitor for cancer prevention. Jornal of Nutrition. 139(12): 2393–2396. https://doi.org/10.3945/jn.109.113332

Horne, J.R. and Vohl, M.C., 2020. Response to the consensus report of the Academy of Nutrition and Dietetics: incorporating genetic testing into nutrition care. Journal of the Academy of Nutrition and Dietetics. 120(12): 1959–1960. https://doi.org/10.1016/j.jand.2020.07.029

Horton, J.D., Goldstein, J.L. and Brown, M.S., 2002. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. Journal of Clinical Investigation. 109(9): 1125–1131. https://doi.org/10.1172/JCI0215593

Howitz, K.T., Bitterman, K.J., Cohen, H.Y., Lamming, D.W., Lavu, S., Wood, J.G., et al., 2003. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. Nature. 425(6954): 191–6. https://doi.org/10.1038/nature01960

Hsu, A., Wong, C.P., Yu, Z., Williams, D.E., Dashwood, R.H. and Ho, E., 2011. Promoter de-methylation of cyclin D2 by sulforaphane in prostate cancer cells. Clinical Epigenetics. 3(1): 3. https://doi.org/10.1186/1868-7083-3-3

Htun, N.C., Suga, H., Imai, S., Shimizu, W. and Takimoto, H., 2017. Food intake patterns and cardiovascular risk factors in Japanese adults: analyses from the 2012 National Health and nutrition survey, Japan. Nutrition Journal. 16(1): 61. https://doi.org/10.1186/s12937-017-0284-z

Hudson, K., Javitt, G., Burke, W. and Byers, P., 2007. ASHG statement: on direct-to-consumer genetic testing in the United States. Obstetrics and Gynecology. 110(6): 1392–1395. https://doi.org/10.1097/01.AOG.0000292086.98514.8b

Hwang, I.K., Lee, C.H., Yoo, K.Y., Choi, J.H., Park, O.K., Lim, S.S., et al., 2009. Neuroprotective effects of onion extract and quercetin against ischemic neuronal damage in the gerbil hippocampus. Journal of Medicinal Food. 12(5): 990–995. https://doi.org/10.1089/jmf.2008.1400

Irimie, A.L., Braicu, C., Pasca, S., Magdo, L., Gulei, D., Cojocneanu, R., et al., 2019. Role of key micronutrients from nutrigenetic and nutrigenomic perspectives in cancer prevention. Medicina (Kaunas). 55(6): 283. https://doi.org/10.3390/medicina55060283

Jenkins, D.J.A., Kendall, C.C.W. and Ransom, T.P.P., 1998. Dietary fiber, the evolution of the human diet and coronary heart disease. Nutrition Research. 18: 633–652. https://doi.org/10.1016/S0271-5317(98)00050-5

Joffe, Y. and Herholdt, H., 2020. What will it take to build an expert group of nutrigenomic practitioners? Lifestyle Genomics. 13(3): 122–128. https://doi.org/10.1159/000507252

Kaviarasan, S., Vijagalakshmi, K. and Anuradha, C.V., 2004. Polyphenol-rich extract of fenugreek seeds protect erythrocytes from oxidative damage. Plant Foods for Human Nutrition. 59(4): 143–147. https://doi.org/10.1007/s11130-004-0025-2

Kelley, N.S., Hubbard, N.E. and Erickson, K.L., 2007. Conjugated linoleic acid isomers and cancer. Journal of Nutrition. 137(12): 2599–2607. https://doi.org/10.1093/jn/137.12.2599

Khan, A., Zaman, G. and Anderson, R.A., 2009. Bay leaves improve glucose and lipid profile of people with type 2 diabetes. Journal of Clinical Biochemistry and Nutrition. 44(1): 52–56. https://doi.org/10.3164/jcbn.08-188

King-Batoon, A., Leszczynska, J.M. and Klein, C.B., 2008. Modulation of gene methylation by genistein or lycopene in breast cancer cells. Environmental and Molecular Mutagenensis. 49(1): 36–45. https://doi.org/10.1002/em.20363

Klopfleisch, R., Klose, P., Weise, C., Bondzio, A., Multhaup, G., Einspanier, R. and Gruber, A.D., 2010. Proteome of metastatic canine mammary carcinomas: similarities to and differences from human breast cancer. Journal of Proteome Research. 9(12): 6380–6391. https://doi.org/10.1021/pr100671c

Kolasa, K.M., 2005. Strategies to enhance effectiveness of individual based nutrition communications. European Journal of Clinical Nutrition. 59 Suppl 1: S24–S30. https://doi.org/10.1038/sj.ejcn.1602171

Koziołkiewicz, M., 2011. Nutrigenomics and nutrigenetics—are they keys for healthy nutrition? In: Conference on Food and Nutrition in 21st Century, Warsaw, 8–9 September 2011.

Krajcovicová-Kudlácková, M., Dusinská, M., Valachovicová, M., Blazícek, P. and Pauková, V., 2006. Products of DNA, protein and lipid oxidative damage in relation to vitamin C plasma concentration. Physiological Research. 55(2): 227–231. https://doi.org/10.33549/physiolres.930761

Kruger, C.L. and Mann, S.W., 2003. Safety evaluation of functional ingredients. Food and Chemical Toxicology. 41(6): 795. https://doi.org/10.1016/S0278-6915(03)00018-8

Kumar, D., 2007a. From evidence-based medicine to genomic medicine. Genomic Medicine. 1(3–4): 95–104. https://doi.org/10.1007/s11568-007-9013-6

Kumar, D., 2007b. Genome mirror. Genomic Medicine. 1(1–2): 87–90. https://doi.org/10.1007/s11568-007-9001-x

Kurzenhauser, S. and Hertwig, R., 2006. How to foster citizen's statistical reasoning: implications for genetic counselling. Community Genetics. 9(3): 197–203. https://doi.org/10.1159/000092657

Lee, W.J. and Zhu, B.T., 2006. Inhibition of DNA methylation by caffeic acid and chlorogenic acid, two common catechol-containing coffee polyphenols. Carcinogenesis, 27: 269–77.

Lee, S.K., Jeon, J.S., Börnke, F., Voll, L., Cho, J.I., Goh, C.H., Jeong, S.W., Park, Y.I., Kim, S.J. and Choi, S.B. et al., 2008. Loss of cytosolic fructose-1,6-bisphosphatase limits photosynthetic sucrose synthesis and causes severe growth retardations in rice (*Oryza sativa*). Plant, Cell & Environment. 31: 1851–1863.

Lee, W.J. and Zhu, B.T., 2006. Inhibition of DNA methylation by caffeic acid and chlorogenic acid, two common catechol-containing coffee polyphenols. Carcinogenesis. 27(2): 269–77. https://doi.org/10.1093/carcin/bgi206

Lee, W.J., Shim, J.Y. and Zhu, B.T., 2005b. Mechanisms for the inhibition of DNA methyltransferase by tea catechins and bioflavonoids. Molecular. Pharmacology. 68(4): 1018–1030. https://doi.org/10.1124/mol.104.008367

Lewis, S.M., Hotchkiss, C.E. and Ullrey, D.E., 2005. Nutrition and nutritional diseases. In: Wolfe-Coote, S., editor. The laboratory primate (Handbook of experimental animals). 1st ed. Elsevier, UK. pp. 181–208. https://doi.org/10.1016/B978-012080261-6/50013-1

Link, A., Balaguer, F. and Goel, A., 2010. Cancer chemoprevention by dietary polyphenols; promising role for epigenetics. Biochemical Pharmacology. 80(12): 1771–1792. https://doi.org/10.1016/j.bcp.2010.06.036

Liu, B. and Qian, S.B., 2011. Translational regulation in nutrigenomics. American Society for Nutrition. 2(6): 511–519. https://doi.org/10.3945/an.111.001057

Lizuka, K., 2017. The transcription factor carbohydrate-response element-binding protein (ChREBP): a possible link between metabolic disease and cancer. Biochimica et Biophysica Acta. 1863(2): 474–485. https://doi.org/10.1016/j.bbadis.2016.11.029

Majid, S., Kikuno, N., Nelles, J., Noonan, E., Tanaka, Y., Kawamoto, K., et al., 2008. Genistein induces the p21WAF1/CIP1 and p16INK4a tumor suppressor genes in prostate cancer cells by epigenetic mechanisms involving active chromatin modification. Cancer Research. 68(8): 2736–2744. https://doi.org/10.1158/0008-5472.CAN-07-2290

Marcu, M.G., Jung, Y.J., Lee, S., Chung, E.J., Lee, M.J., Trepel, J., et al., 2006. Curcumin is an inhibitor of p300 histone acetyltransferase. Medicinal Chemistry. 2(2): 169–174. https://doi.org/10.2174/157340606776056133

Marteau, T.M., 1999. Communicating genetic risk information. British Medical Bulletin. 55(2): 414–428. https://doi.org/10.1258/0007142991902466

Mead, N., 2007. Nutrigenomics: the genome–food interface. Environmental Health Perspectives. 115(12): A582–A589. https://doi.org/10.1289/ehp.115-a582

Mitall, B.K. and Garg, S.K., 1995. Anticarcinogenic, hypocholesterolemic, and antagonistic activities of *Lactobacillus acidophilus*. Critical Reviews in Microbiology. 21(3): 175–214. https://doi.org/10.3109/10408419509113540

Mitra, B., Guha, D. and Gangopadhya, P.K., 2005. Nutrigenomics: a new frontier. [cited 2011 Jan 25]. Available from: http://www.apiindia.org/images/stories/pdf/medicine_update_2005/chapter_182.pdf

Mohan, V., Sandeep, S., Deepa, R., Shah, B. and Varghese, C., 2007. Epidemiology of type 2 diabetes: Indian scenario. Indian Journal of Medical Research. 125: 217–230.

Müller, M. and Kersten, S., 2003. Nutrigenomics: goals and strategies. Nature Reviews Genetics. 4(4): 315–322. https://doi.org/10.1038/nrg1047

Murray, T.H. and Botkin, J.R., 1995. Genetic testing and screening: ethical issues. In: Reich, W.T., editor. Encyclopedia of bioethics. New York: Simon & Schuster Macmillan Publishers. pp. 1005–1111.

Myzak, M.C., Karplus, P.A., Chung, F.L. and Dashwood, R.H., 2004. A novel mechanism of chemoprotection by sulforaphane: inhibition of histone deacetylase. Cancer Research. 64(16): 5767–5774. https://doi.org/10.1158/0008-5472.CAN-04-1326

Neeha, V.S. and Kinth, P., 2013.Nutrigenomics research: a review. Journal of Food Science and Technology. 50(3): 415–428. https://doi.org/10.1007/s13197-012-0775-z

Nian, H., Delage, B., Pinto, J.T. and Dashwood, R.H., 2008. Allyl mercaptan, a garlic-derived organosulfur compound, inhibits histone deacetylase and enhances Sp3 binding on the P21WAF1 promoter. Carcinogenesis. 29(9): 1816–1824. https://doi.org/10.1093/carcin/bgn165

Nielsen, D. E. and El-Sohemy, A., 2012. A randomized trial of genetic information for personalized nutrition. Genes and Nutrition. 7(4): 559. https://doi.org/10.1007/s12263-012-0290-x

Nijveldt, R.J., Van Nood, E., Van Hoorn, D.E., Boelens, P.G., Van Norren, K. and Van Leeuwen, P.A., 2001. Flavonoids: a review of probable mechanisms of action and potential applications. The American Journal of Clinical Nutrition. 74(4): 418–425. https://doi.org/10.1093/ajcn/74.4.418

Ohlhorst, S.D., Russell, R., Bier, D., Klurfeld, D.M., Li, Z., Mein, J.N., et al., 2013. Nutrition research to affect food and a healthy life span. Journal of Nutrition. 98(2): 620–625. https://doi.org/10.3945/ajcn.113.067744

Olaharski, A.J., Rine, J., Marshall, B.L., et al., 2005. The flavouring agent dihydrocoumarin reverses epigenetic silencing and inhibits sirtuin deacetylases. PLoS Genetics. 1(6): e77.

Orlikova, B., Schnekenburger, M., Zloh, M., Golais, F., Diederich, M. and Tasdemir, D., 2012. Natural chalcones as dual inhibitors of HDACs and NF-kappaB. Oncology Report. 28(3): 797–805. https://doi.org/10.3892/or.2012.1870

Palou, A., 2007. From nutrigenomics to personalised nutrition. Genes and Nutrition. 2(1): 5–7. https://doi.org/10.1007/s12263-007-0022-9

Paluszczak, J., Krajka-Kuzniak, V. and Baer-Dubowska, W., 2010. The effect of dietary polyphenols on the epigenetic regulation of gene expression in MCF7 breast cancer cells. Toxicology Letters. 192(2): 119–125. https://doi.org/10.1016/j.toxlet.2009.10.010

Park. S. S., Skaar, D. A., Jirtle, R. L. and Hoyo, C., 2017. Epigenetics, obesity and early-life cadmium or lead exposure. Epigenomics. 9(1): 57–75.

Peregrin, T., 2001. The new frontier of nutrition science: nutrigenomics. Journal of the American Dietetic Association. 101(11): 1306. https://doi.org/10.1016/S0002-8223(01)00309-1

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., et al., 2017. Oxidative stress: harms and benefits for human health. Oxidative Medicine and Cellular Longevity. 2017: 8416763. https://doi.org/10.1155/2017/8416763

Rahman, A., Chakraborty, S. and Kabir, Y., 2020. Harnessing personalized nutrigenomics for cancer prevention and treatment through diet-gene interaction In: Functional foods in cancer prevention and therapy. Kabir, Y., editor. Elsevier, UK. pp. 387–403. https://doi.org/10.1016/B978-0-12-816151-7.00019-3

Raj, M., Sundaram, K.R., Paul, M., Deepa, A.S. and Kumar, R.K., 2007. Obesity in Indian children: time trends and relationship with hypertension. The National Medical Journal of India. 20(6): 288–293.

Ramos-Lopez, O., Milagro, F.I., Allayee, H., Chmurzynska, A., Choi M.S., Curi R., et al., 2017. Guide for current nutrigenetic, nutrigenomic, and nutriepigenetic approaches for precision nutrition involving the prevention and management of chronic diseases associated with obesity. Journal of Nutrigenetics and Nutrigenomics. 10(1–2): 43–62. https://doi.org/10.1159/000477729

Rastogi, S., Pandey, M.M., and Rawat, A.K.S., 2017. Spices: therapeutic potential in cardiovascular health. Current Pharmaceutical Design. 23(7): 989–998. https://doi.org/10.2174/1381612826661610210160009

Reddy, V.S., Palika, R., Ismail, A., Pullakhandam, R. and Reddy, G.B., 2017. Nutrigenomics: opportunities & challenges for public health nutrition. Indian Journal of Medical Research. 148(5): 632–641. https://doi.org/10.4103/ijmr.IJMR_1738_18

Reecy, J.M., Spurlock, D.M. and Stahl, C.H., 2006. Gene expression profiling: insights into skeletal muscle growth and development. Animal Science Journal. 84 Suppl: E150–E154. https://doi.org/10.2527/2006.8413_supplE150x

Reen, J.K., Yadav, A.K. and Singh, J., 2015. Nutrigenomics: concept, advances and applications. Asian Journal of Dairy & Food Research. 34(3): 205–212. https://doi.org/10.5958/0976-0563.2015.00041.X

Riscuta, G., 2016. Nutrigenomics at the interface of aging, lifespan, and cancer prevention. Journal of Nutrition. 146(10): 1931–1939. https://doi.org/10.3945/jn.116.235119

Ronteltap, A., van-Trijp, J.C.M. and Renes, R.J., 2009. Consumer acceptance of nutrigenomics-based personalised nutrition. British Journal of Nutrition. 101(1): 132–144. https://doi.org/10.1017/S0007114508992552

Roosan, D., Wu, Y., Tran, M., Huang, Y., Baskys, A. and Roosan, M.R., 2022. Opportunities to integrate nutrigenomics into clinical practice and patient counseling. European Journal of Clinical Nutrition. https://doi.org/10.1038/s41430-022-01146-x

Roy, S., Bagchi, D., Bagchi, M., Khanna, S., Sen, C.K., Rink, C., et al., 2004. Body weight and abdominal fat gene expression profile in response to a novel hydroxycitric acid–based dietary supplement. Gene Expression. 11(5–6): 251–262. https://doi.org/10.3727/000000003783992289

Sacks, F. M. and Katan, M., 2002. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. The American Journal of Medicine. 113 Suppl 9B: 13–24. https://doi.org/10.1016/S0002-9343(01)00987-1

Sales, N.M.R., Pelegrini, P.B. and Goersch, M.C., 2014. Nutrigenomics: definitions and advances of this new science. Journal of Nutrition and Metabolism. 2014: 202759. https://doi.org/10.1155/2014/202759

Sanhueza, J. and Valenzuela, A.B., 2012. Nutrigenomics: revealing the molecular aspects of a personalized nutrition. Chilean Magazine of Nutrition. 39: 71–85.

Savini, I., Gasperi, V. and Catani, V.M., 2016. Nutrigenetics. Chichester: John Wiley & Sons. pp. 1–11. https://doi.org/10.1002/9780470015902.a0021028

Schafer, Z.T. and Cockfield, J.A., 2019. Antioxidant defences: a context-specific vulnerability of cancer cells. Cancers (Basel). 11(8): 1208. https://doi.org/10.3390/cancers11081208

Schuster, G.U., 2006. Nutrients and gene expression. In: Kaput, J. and Rodriguez, R.L., editors. Nutritional genomics. Hoboken, NJ: Wiley & Sons. pp. 153–170. https://doi.org/10.1002/0471781797.ch7

Shu, L., Khor, T.O., Lee, J.H., Boyanapalli, S.S., Huang, Y., Wu, T.Y., et al., 2011. Epigenetic CpG demethylation of the promoter and reactivation of the expression of Neurog1 by curcumin in prostate LNCaP cells. The AAPS Journal. 13(4): 606–614. https://doi.org/10.1208/s12248-011-9300-y

Siddique, R.A., Tandon, M., Ambwani, T., Rai, S.N. and Atreja, S.K., 2009. Nutrigenomics: nutrient–gene interactions. Food Reviews International. 25(4): 326–345. https://doi.org/10.1080/87559120903155883

Sorensen, M., Jensen, B.R., Poulsen, H.E., Deng, X., Tygstrup, N., Dalhoff, K., et al., 2001. Effects of a Brussels sprouts extract on oxidative DNA damage and metabolising enzymes in rat liver. Food Chemistry and Toxicology. 39(6): 533–540. https://doi.org/10.1016/S0278-6915(00)00170-8

Speroni, E., Cervellati, R., Dall'Acqua, S., Guerra, M.C., Greco, E., Govoni, P., et al., 2011. Gastroprotective effect and antioxidant properties of different *Laurus nobilis* L. leaf extracts. Journal of Medicinal Food. 14(5): 499–504. https://doi.org/10.1089/jmf.2010.0084

Srinivasan, K., 2013. Dietary spices as beneficial modulators of lipid profile in condition of metabolic disorders and disease. Food and Function. 4(4): 503–521. https://doi.org/10.1039/c2fo30249g

Stavinoha, R.C. and Vattem, D.A., 2015. Potential neuroprotective effects of cinnamon. International Journal of Applied Research in Natural Prodocuts. 8: 24–46.

Stefanska, B., Rudnicka, K., Bednarek, A. and Fabianowska-Majewska, K., 2010. Hypo methylation and induction of retinoic

acid receptor beta 2 by concurrent action of adenosine analogues and natural compounds in breast cancer cells. European Journal of Pharmacology. 638(1–3): 47–45. https://doi.org/10.1016/j.ejphar.2010.04.032

Stevenson, M., 1999. Commercializing safety and efficacy of home genetic tests. Journal of Biolaw and Business. 3(1): 29–39.

Surendran, S., Adaikalakoteswari, A., Saravanan, P., Shatwaan, I.A., Lovegrove, J.A. and Vimaleswaran, K.S., 2018. An update on vitamin B12-related gene polymorphisms and B12 status. Genes and Nutrition. 13: 2. https://doi.org/10.1186/s12263-018-0591-9

Syvertsen, C., Halse, J., Hoivik, H.O., Gaullier, J.M., Nurminiemi, M., Kristiansen, K., et al., 2007. The effect of 6 months supplementation with conjugated linoleic acid on insulin resistance in overweight and obese. International Journal of Obesity. 31(7): 1148–1154. https://doi.org/10.1038/sj.ijo.0803482

Szymczak-Pajor, I. and Sliwinska, A., 2019. Analysis of association between vitamin D deficiency and insulin resistance. Nutrients. 11(4): 794. https://doi.org/10.3390/nu11040794

Tan, S., Wang, C., Lu, C., Zhao, B., Cui, Y., Shi, X., et al., 2009. Quercetin is able to demethylate the p16INK4a gene promoter. Chemotherapy. 55(1): 6–10. https://doi.org/10.1159/000166383

Tchombe, N.L., Louajri, A. and Benajiba, M.N., 2012. Therapeutical effects of ginger. ISESCO Journal of Science and Technology. 8: 64–69.

Thomas, P. and Fenech, M., 2009. Folate and vitamins B2, B6, and B12. In: Knasmüller, S., DeMarini, D.M., Johnson, I. and Gerhäuser, C., editors. Chemoprevention of cancer and DNA damage by dietary factors. John Wiley & Sons, US. pp. 417–433. https://doi.org/10.1002/9783527626588.ch25

Utkina, A.S. and Karagodin, V.P., 2021. Nutrigenomics as a tool for optimizing the composition of specialized food products by the efficiency criterion. IOP Conference Series: Earth and Environmental Science. 677: 042050. https://doi.org/10.1088/1755-1315/677/4/042050

Uyeda, K., Yamashita, H. and Kawaguchi, T., 2002. Carbohydrate responsive element binding protein (ChREBP): a key regulator of glucose metabolism and fat storage. Biochemical Pharmacology. 63(12): 2075–2080. https://doi.org/10.1016/S0006-2952(02)01012-2

van Ommen, B. and Stierum, R., 2002. Nutrigenomics: exploiting systems biology in the nutrition and health arena. Current Opinion in Biotechnology. 13(5): 517–521. https://doi.org/10.1016/S0958-1669(02)00349-X

Vidal, D.R., 2009. Transgenics, nutrigenetics and nutrigenomics in food. Food Science and Technology. 11(1): 10–12.

Vineis, P. and Christiani, D.C., 2004. Genetic testing for sale. Epidemiology. 15(1): 3–5. https://doi.org/10.1097/01.ede.0000101961.86080.f8

Wang, T., Feugang, J.M., Crenshaw, M.A., Regmi, N., Blanton, J.R. and Liao, S.F., 2017. A systems biology approach using transcriptomic data reveals genes and pathways in porcine skeletal muscle affected by dietary lysine. International Journal of Molecular Science. 18(4): 885. https://doi.org/10.3390/ijms18040885

Weng, C.Y., Wang, C.E., Xie, W.B., Xu, S.Y., Wang, Y.J. and Zheng, Y.G., 2021. Comparative proteome analysis of *Actinoplanes utahensis* grown on various saccharides based on 2D-DIGE and MALDI-TOF/TOF-MS. Journal of Proteomics. 239: 104193. https://doi.org/10.1016/j.jprot.2021.104193

Yamashita, H., Takenoshita, M., Sakurai, M., Bruick, R.K., Henzel, W.J., Shillinglaw, W., et al., 2001. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. Proceedings of the National Academy of Sciences of the United States of America. 98(16): 9116–9121. https://doi.org/10.1073/pnas.161284298

Yan, M., Song, Y., Wong, C.P., Hardin, K. and Ho, E., 2008. Zinc deficiency alters DNA damage response genes in normal human prostate epithelial cells. Journal of Nutrition. 138(4): 667–673. https://doi.org/10.1093/jn/138.4.667

Yang, Y., Liu, L., Naik, I., Braunstein, Z., Zhong, J. and Ren, B., 2017. Transcription factor C/EBP homologous protein in health and diseases. Frontiers in Immunology. 8: 1612. https://doi.org/10.3389/fimmu.2017.01612

Zhang, C., 2014. Essential functions of iron-requiring proteins in DNA replication, repair and cell cycle control. Protein & Cell. 5(10): 750–760. https://doi.org/10.1007/s13238-014-0083-7

Zhang, P., McGrath, B.C., Reinert, J., Olsen, D.S., Lei, L., Gill, S., et al., 2002. The GCN2 eIF2α kinase is required for adaptation to amino acid deprivation in mice. Molecular and Cell Biology. 22(19): 6681–6688. https://doi.org/10.1128/MCB.22.19.6681-6688.2002