The Annals of the University Dunarea de Jos of Galati
Fascicle VI – Food Technology (2018), 42(2), 168-184

REVIEW PAPER

GENOMICS ERA IN THE NUTRITION FIELD

LEONTINA GRIGORE-GURGU

Faculty of Food Science and Engineering, Dunarea de Jos University of Galati., 111 Domneasca Street, 800201, Galati, Romania
*Corresponding author: lili_gurgu@yahoo.com

Received on 1st November 2018
Revised on 25th November 2018

Nutritional deficiencies or the imbalance between food ingestion and physical inactivity correlated with a genetic susceptibility are the main cause for disease development. This review discusses the basic concepts of nutrigenetics and nutrigenomics and offers a few examples of genes polymorphisms in relation with human predisposition to disease according to its diet. These two new 'omic' technologies use complex sources of investigation in order to develop mechanisms through it would be easy to explain the genetic basis of interindividual differences in response to the same nutrient. Moreover, there are presented the anticarcinogenic and antioxidative activities of some biologically active compounds and the used mechanisms for maintaining cell homeostasis.

Keywords: genes polymorphisms, nutrigenomics, metabolic syndrome, cancer, biologically active compounds

Introduction

In the last decade, nutrition and human genome were interconnected resulting new research fields, nutrigenetics and nutrigenomics, both being very promising for the human health′ solutions.

When the scientists analysis the response of gene variants to nutrients and relates these variations to disease states, it can speak about nutrigenetics or "personalized nutrition" (Simopoulos, 2010; Kohlmeier *et al*., 2016; Sharma and Dwivedi, 2017; German *et al*., 2011). On the other hand, when the studies are based on the influence of the nutrients (vitamins, minerals, carbohydrates, fats and proteins) on gene expression regulation, it can speak about nutrigenomics.

The association between nutrients and human health is a primordial one, which is now studied by novel epidemiological techniques. The environmental factors, the socio-economic status together with the micro- and macronutrients are involved in genes expression regulation and play a specific role in determining the human health.

There are two-ways of interaction between nutrients and genes: from nutrients to genes expression and metabolic responses and then, from the health condition to

susceptibility to appear the disease state based on what is happened in the human genome.

First, it is interesting to analyse how the polymorphism change the metabolic response to diet and influence the risk patterns of disease. In the human population genome occur natural genetic variations that are called polymorphisms. When the variation take place at a single base pair cause a single nucleotide polymorphism (SNP) which define the risk of each person to disease, nutrient variation requirements and emphasizes the gene variability (of different individuals) to the same nutrient.

On the other hand, nutrients act directly or indirectly to DNA and, in consequence to gene expression in terms of: transcription, or translation process, influencing proteins biosynthesis.

The main important aspect of nutrigenetics and nutrigenomics could be the process of specific dietary programmes development based on individual genotype in order to promote the health and to have a better management of chronic diseases.

This review is focused on some specific examples of association between gene polymorphisms and human diseases, correlated with specific food components.

Interdependence between MTHFR Gene Polymorphisms and Human Diseases

Each individual is unique due to variability existing in its genome. Existence of variation in the gene copy number, the chromosomal rearrangements, deletions, insertions or the presence of nucleotide polymorphisms offer to each person a predisposition to disease, in the context of environment factors - nutrient – gene interaction.

Microarray technology was used in studies of human single nucleotide polymorphisms (SNPs) and was able to provide results that were correlated with a specific disease or trait or with some ethnicity.

Nutrigenetics studies offered answers to the oldest question: why and how people reveal different physiology responses to the same nutrient? Thus, the nutrigenetics made possible the correlation between genetic differences that influenced the individual response to diet.

In the scientific literature the main example of nutrigenetics is the response of methylene-tetra-hydro folate reductase gene (MTHFR) to folic acid. The encoded enzyme of MTHFR catalyses the transformation of 5,10-methylenetetrahydrofolate (5,10-MTHF) to 5-methyltetrahydrofolate (5-MTHF), which is a methyl donor for DNA methylation, and also a co-substrate for re-methylation of homocysteine (Fohr *et al*., 2002). Abnormal folate metabolism, some vascular disease, neural tube errors, Down syndrome, colon cancer or acute leukaemia were associated with genetic variations in this gene.

Computation analysis of each non-synonymous SNP (nsSNP) of MTHFR gene revealed that R157Q (substitution of arginine from 157 position with glutamine), L323P (substitution of leucine from 323 position with proline) and W500C (substitution of tryptophan from 500 position with cysteine) are the most

deleterious SNP affecting protein stability and also the interaction of ligand molecules with MTHFR protein (Desai and Chauhan, 2018).

Another two SNPs variants of MTHFR gene, A222V (alanine from 222 position was substituted with valine) and E429A (glutamic acid from 429 position was substituted with alanine), were associated with Down syndrome, intellectual disability (Saccucci *et al.*, 2008; Coppedè, 2015; Desai and Chauhan, 2016b) or with a risk factor for spontaneous abortions and decreased fetal viability, respectively (Stover, 2004).

Moreover, other polymorphism in the exon-4 region of this gene (the rs1801133 – the substitution of alanine by valine) has been correlated with the symptomatology of ischemic stroke (IS) *(*Shi *et al., 2018)*. It is known that, the encoded enzyme, MTHFR plays a crucial role in total homocysteine (tHcy) metabolism, which can activate MAP (Mitogen-activated protein) Kinase signaling by a broad range of stimuli, one of them being the excessive production of reactive oxygen species (ROS). Because, MAP kinase pathway is involved in a variety of cellular processes like motility, stress response, or apoptosis (Arthur and Ley, 2013; Cargnello and Roux, 2011) it is possible that the tHcy accumulation to produce death in the arterial and venous endothelial cells.

Nojima *et al.* (2018) showed that the individuals with different MTHFR gene polymorphisms demonstrate lower DNA methylation degree when plasma folate level is low whereas for the individuals with a normal MTHFR activity, the DNA methylation level is keep up irrespectively of plasma folate level. The explanation that the authors offered was based on the presence of other DNA methylation determinants, like alcohol intake, that can modify the relation between folate intake and global DNA methylation levels, respectively (Ono *et al*., 2012). More exactly, it was observed a complex association between alcohol consumption, C reactive protein (CRP) level and DNA methylation among individuals carrying the minor allele of the MTHFR rs1801133 missense SNP (Nojima *et al*., 2018).

Polymorphisms of Peroxisome Proliferator Activated Receptors (PPARs) and their Consequences on Human Health

Peroxisome Proliferator-Activated receptors were discovered in the early 90s and then, 20 years later, many articles arose on this topic. PPARs are found in the peroxisomes, a single membrane subcellular organelles, where fulfil important functions, being involved not only in the peroxisomal metabolism but also in the lipid one.

Actually, there are three isoforms: PPAR-α, PPAR-δ, and PPAR-γ, included to the superfamily of nuclear receptors. Each of them having its own functionality in accordance with cells distribution, as follows: PPAR-α is expressed predominantly in cells with active fatty acid catabolism (like: liver cells, enterocytes, non-neuronal cells, vascular and immune cell types) (Moreno et al., 2004; Heneka and Landreth, 2007), whereas the PPAR-δ/β were found in skin, skeletal muscle, adipocytes, macrophages, and brain (Barish *et al*., 2006; Tyagi *et al.*, 2011).

The resulting consequences in case of abnormalities in PPARs functions are huge if it can be considered their role in genes modulation, their control on lipid and glucose metabolism, or their involvement in gluconeogenesis, and glycogenolysis pathways (Vamecq *et al*., 2014).

It have been studied the influence of two PPARs polymorphisms (PPAR-δ A/G and PPAR-δ C/G) on the anthropometric and blood measurements in response to exercise-centered lifestyle intervention in Japanese middle-aged men. The results showed that the anthropometric parameters and clinical blood measurements were not significantly different among the two tested SNPs (Nishida *et al*., 2018).

Furthermore, Ke *et al*., (2016) investigated (using Asian data sets from Singapore), if the interaction between 53 common SNPs, found in the PPAR-α/δ/γ, with other genetic variants across the genome, effects plasma high-density lipoprotein-cholesterol (HDL-C) levels. The study is based on the fact that, HDL-C level is inverse correlated with risk of coronary heart disease. An increase of HDL-C of only 10 $mg \cdot L^{-1}$ is possible to induce a risk reduction of 2–3% (Gordon *et al.*, 1977; Ali *et al*., 2012).

The study of Ke *et al*. (2016) provides, for the first time, that the interaction between PPAR-δ, SNP rs2267668 and the epithelial membrane protein 2 (*EMP2*), SNP rs7191411, cause an increase of HDL-C levels in the Singaporean Chinese population who are carrying minor alleles from both SNPs. Moreover, the result of the interaction between PPAR-δ and EMP2 is a reverse cholesterol transport, from peripheral tissues back to the liver, which has a relevant biological meaning.

In general, physical exercises activate the transcription factors, PPAR-γ and LXRα (Liver X Receptor), that increase the FAT-CD36 (Fatty Acid Translocase), ABCA1 (ATP Binding Cassette Subfamily A Member 1), and ABCG1 (ATP-binding cassette sub-family G member 1) gene expression, (genes which encode the cholesterol-related reverse transporters).

The hypocaloric diets, a replacement of carbohydrates by lipids, the functional foods and bioactive compounds offer an increased HDL-C level, improve its functionality, promote a better metabolic profile and decrease the risk of atherosclerotic cardiovascular diseases (Siri-Tarino, 2011; Chen *et al.*, 2014; Farràs *et al*., 2015; Hernáez *et al*., 2016; Rondanelli *et al*., 2016; Marques *et al.*, 2018).

Because PPAR-δ was also linked with type 2 diabetes mellitus (T2DM), Raj *et al.*, (2017) analysed its role on early and late onset of T2DM, in North Indian population. They found that polymorphisms, Pro12Ala of PPAR-δ, intron7 polymorphism of PPAR-α and T + 294C polymorphism of PPAR- δ are significant connected with T2DM at the subjects which have more than 25 years from disease onset.

Even T2DM particularly depends on diet and lifestyle, it was observed an inverse correlation between the distribution of Ala allele (from Pro12Ala polymorphism of PPAR-δ) frequency in the European populations and T2DM prevalence (Scacchi *et al*., 2007). The present pattern seems to have a descending distribution, from northern to southern populations, depended on the temperature and on the diet rich

in lipids. In Table 1 are presented many others examples of polymorphisms and their effects as an outcome of gene-diet interaction.

Table 1. Examples of gene-dyet interaction effects

Gene affected /Genotype	SNPs	Effects of gene expression	Susceptible or tested population	Dietary	References
Peroxisome Proliferator-Activated Receptor Delta -PPARD	rs7770619	Type 2 diabetes (T2D)	Korean	Diet rich in unsaturated fat	Kim *et al*., 2018
Cholesterol transport gene - *ABCG5*	rs6720173	Significant variability in the cholesterol responsiveness	Healthy people carrying the SNPs	High-PUFA diet	Abdullah *et al*. 2016; Abdullah *et al.*, 2018; Hubacek *et al.*, 2003
Bile acid synthesis- *CYP7A1*	rs3808607			Lower intake of red meat, animal fat, and eggs	
Cholesterol synthesis gene *DHCR7*	rs760241			Dietary products	
9p21 variants	rs10757274 rs10757278 rs2383206 rs1333049 rs4977574	Cardiovascular disease (CVD)	Women, young adults from different ethnocultural groups	CVD risk can be reduced by a diet high in raw vegetables and fruits, or by higher vegetable, and wine intake	Do *et al*., 2011; Hindy *et al.*, 2012;
Apolipoprotein A5- APOA5	rs662799 rs2075291	*Low level of adiponectin*, Higher risk of *atherosclerosis*	Korean people with low HDL-cholesterol levels	High saturated fatty acid consumption	Kim *et al*., 2018
LDL Receptor - LDLR	rs2569556	Autosomal Dominant Hypercholesterolemia	Asian with high LDLc levels	CHO and fat	Lye *et al*., 2013
Protein convertase subtilisin/ kexin type 9 - PCSK9	rs565436				
Apolipoprotein E -APOE	rs405509	Higher TC, LDL-C or TAG levels, lower HDL-C levels	Inuit	High Total fat and saturated fat intake	Rudkowska *et al*., 2013
ATP binding cassette subfamily A member 1- ABCA1	rs9282541	Low HDL, Tangier disease	Mexican Mestizos	4 weeks of LSF followed by 8 weeks of LSF+SSF	Acuña-Alonzo *et al.*, 2010; Guevara-Cruz *et al*., 2010

	rs2230806 (R219K)	Higher HDL-C level, Lower risk of cardiovascular disease for R219K carriers	Asian	6597 cases and 15,369 controls found in different publications (data analysis)	Jung *et al.*, 2018; Ma *et al.*, 2011
Dedicator of Cytokinesis 7 - DOCK7 Finc Finger - ZPR1/ZNF259 Finc Finger - ZNF664	rs645040 rs964184 rs4765127	Increased risk for chronic metabolic disease	Children and adults	High consumption of sugar-sweetened beverages	Haslam *et al.*, 2017; Sonestedt *et al.*, 2015
Alpha-ketoglutarate dependent dioxygenase - FTO	rs1121980 rs9939609	Adiposity, Genetic predisposition to obesity Association with body mass index, obesity and a predisposition to T2D	Data from three cohorts Adults with morbid obesity; Romanian obese children	Intake of sugar-sweetened beverages Low physical inactivity, preferences for high caloric density in foods	Olsen *et al.*, 2016 Frayling *et al.* 2007; Simopoulos, 2010; Duicu *et al.*, 2016
FTO-associated noncoding variants - ARID5B, (IRX3 and IRX5 are repressed)	rs1421085	Adipocyte browning, lipid storage, and fatty acid oxidation	Epigenomics data from human cell lines	High fat diet	Claussnitzer *et al.*, 2015
Glucokinase regulatory protein gene - *GCKR*	rs1260326, rs780094	T2D and MetS	European population, Japanese population	Not specified	Kim *et al.*, 2018; Onuma *et al.*, 2010
Hephaestin like 1 - HEPHL1	rs7946162 rs2460063 rs7127348	Colorectal cancer (CRC)	Adults with these SNPs	High Iron intake	Nicholas *et al.*, 2013
Solute Carrier Family 30 Member 8-SLC30A8	rs13266634	T2D	Postmenopausal women	Zn intake	Goyal *et al.*, 2010
Glutathione peroxidase 1 - GPX1; Superoxide dismutase 2 - SOD2	rs1050450	Prostate cancer risk	Nested case control study as a part of the Physicians Health Study, carried out in a large number of US population	Nutritional Selenium deficiency	Torrens *et al.*, 2006
Aldehyde dehydrogenase 2 -ALDH2	rs671	Facial flushing and severe hangovers	Individuals with either one or two copies of the A-allele	Higher alcohol intake	Takeuchi *et al.* 2011; Wang *et al.* 2013

Vitamin D receptor - VDR	rs2228570 rs1544410	Skin cancer risk, Colorectal cancer risk	Caucasians, Asians, Africans	Low calcium intake, energy intake, energy expenditure	Raimondi *et al.*, 2009
Endothelial nitric oxide synthase - eNOS	rs2070744 rs1799983	Vascular and renal disease risk, susceptibility to diabetic nephropathy	South Indian Systemic lupus erythematosus patients	Not specified	Dong *et al*., 2018
Long-chain acyl CoA synthetase 1 – ACLS1	rs9997745 rs12503643	Metabolic syndrome	Cohort of 13,000 adults selected from an existing French SU.VI.MAX	Fatty acid intake	Phillips *et al*., 2010
Leptin receptor - LEPR	rs1137101 rs1137100	Hypertension or lipid abnormality	Older Han adults from China	Not specified	Wu *et al.*, 2016

Nutrigenomics and Diet Reach in Omega-6/Omega-3 Fatty Acids

Nutrigenomics, as a subset of genomics field, use multiple disciplines and establish the effects of ingested nutrients on genome stability, epigenome alterations, transcriptome, proteome and metabolome.

Nutrigenomics have an important role to identify the genes that are expressed/repressed after food ingestion and also, to analyse the response of polymorphisms to diet. Based on these results will be possible to determine the individual nutritional requirement, a personalized diet, mainly to help each person in preventing the chronic diseases manifestation (Nielsen and El-Sohemy, 2012; Kirwan *et al*., 2016; de Toro-Martín *et al*., 2017).

It is significant to understand all the events that take place in cells at posttranscriptional levels and to analyse, in a complex manner, using bioinformatics software, the metabolism pathways of each person in order to obtain the ideal diet that will provide the nutritional value for maintaining the health or to help the body to heal.

Such intelligent interventions will bring a new vision on human diet management, will recommend foods, supplements, and lifestyle modifications for each person based on the personal sensory preferences or intolerances to foods. Of course that, the effects of nutrients should be correlated with the physiological processes, including food digestion, nutrients and vitamins transport, cellular metabolism and with the activation of transcriptional factors.

Worldwide, many people are suffering from metabolic syndrome (MetS) and their number increases (Cameron *et al*. 2004). MetS is a consequences of urbanization, of sedentary lifestyle and obesity and is linked with the risk of developing cardiovascular diseases (like, atherosclerosis, hypertension, and thrombosis), type 2 diabetes mellitus or cancer.

In western diets because of a modern agriculture, the ratio between omega-6 and omega-3 polyunsaturated fatty acids (PUFA) achieve 20:1, instead of 1:1, (Simopoulos, 2003; 2008; 2013; Kang, 2003; Donahue, 2011; Kromhout and de Goede, 2014). In order to avert obesity, Simopoulos (2016), concluded that, a balanced omega-6: omega-3 ratio of 1–2:1 is one of the most important dietary factors for health maintaining. Instead, for Chinese population, in order to lower the risk of total mortality, the ratio ranging 6:10 may be a solution (Zhuang et al., 2018).

While omega-3 fatty acids derivatives have strong anti-inflammatory effects, and are involved in controlling the apoptosis, or in lymphocyte proliferation, the omega-6 fatty acids is pro-inflammatory (de Pablo and Alvarez de Cienfuegos, 2000; Kruger *et al*. 2010; Wymann and Schneiter, 2008).

In recent years, new studies offered epidemiologic evidence on the fact that n-6:n-3 ratio is obsolete and non-specific and also that, a consistent dietary cannot be given stand on it (Mensink et al., 2003; Chowdhury *et al*., 2014; Harris, 2018; Zhuang *et al*., 2018). The base of these observations is the reason that, while two saturated fatty acids, (palmitic and stearic), both from the same class, have shown antagonic physiological effects, there are some trans monounsaturated fatty acids, from different classes, with more similar effects. In his review, Harris (2018) brings to discussion four assumptions underlying why this metric is questionable and offered a new metric to n-6:n-3 ratio, called the Omega-3 Index, which represents the sum of eicosapentaenoic and docosahexaenoic acids in red blood cell membranes expressed as a percent of total fatty acids (Harris *et al*., 2013; Harris, 2018).

Both omega-6 and omega-3 fatty acids influence gene expression. Szostak *et al.*, (2016) investigated, using RNA-Seq analysis, the physiological effects of increased dietary intake of omega-6 and omega-3 fatty acids. The results highlighted a reduced expression of CYP7A1 gene (Cytochrome P450 Family 7 Subfamily A Member 1), which is one of the target genes of LXR (Liver X Receptor), suggesting a major down-regulation of lipid metabolism and an increase of β-oxidation (Ramayo-Caldas *et al*. 2012; Szostak *et al.*, 2016). Furthermore, the expression of fatty acid desaturase (FADS) cluster, which act predominantly in the omega-3 metabolic pathway, increases (Ratnayake and Galli, 2009). The biological meaning is a higher absorption and storage, or lower degradation of omega-3 fatty acids in detriment of omega-6 fatty acids (Szostak *et al*., 2016).

Nutrigenomics and Diet Reach in Biologically Active Compounds for Cancer Prevention

When a cell is getaway from the genes control, its growth and division become uncontrollably. Consequently, the cell is dividing more rapidly forming a tumor, which is more resistant to the controls that maintain the equilibrium between proliferation and suppression. Most cancers are the results of gene mutations and are associated, according to epidemiological data, with lifestyle diet. The natural compounds have the potential to interfere with the early or later tumorigenesis stages influencing tumor behavior. Nutrigenomics study the gene expression after

interaction with bioactive compounds or nutrients, being part of cancer management. It is known that some food compounds interfere with the epigenome but the molecular mechanisms is not well understood, even that some progresses were made.

Moreover, there are some geographical areas where the incidence for specific tumors, in the same population, is higher compare with others, which means that genome background alone does not justify the susceptibility for one or other tumor types (Cook *et al.*, 1999; Imai *et al*., 1997). So, the dietary and environmental factors, together with endogenous reactions could initiate the tumorigenesis process.

Resveratrol and quercetin, flavonoids, lutein, lycopene or other carotenoids are biologically active substances that were used for hundreds of years in traditional medicine for chemoprevention and therapy.

Resveratrol found in many plants (e.g. grapes, peanuts, berries or plums) proved to have anticancer activity by suppressing some microRNAs that are usually involved in human colon and prostate cancer (Tili *et al*. 2010; Dhar *et al.* 2011).

Flavonoids are known as gene modulators in signalling pathways in different cancer types, like: breast, colon, prostate, or ovarian (Weng *et al.*, 2012; Omene *et al*., 2013; Du *et al*., 2011; Wubetu *et al*., 2016). Epigallocatechin-3-gallate (EGCG) is found in green tea, represents more than 50% of the total polyphenols, and has the ability to induce apoptosis in the human breast cancer cells by inhibition of the human telomerase reverse transcriptase (*hTERT)* or the activity of DNA methyltransferases (DNMTs) and histone acetyltransferases (HATs). The effects are: hypo methylation of the DNA and histone deacetylation, both processes contributing to inhibition of *hTERT* expression, and consequently to cellular apoptosis (Meeran *et al.*, 2011).

Genistein is a natural isoflavone found in fava beans, lupins, or soybeans. It has anticarcinogenic and antioxidative effects, and inhibits angiogenesis and metastasis in breast, gastric, lung, pancreatic, renal, and melanoma cancer (Kaufman *et al*., 1997; Banerjee et al., 2008) by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-*κ*appa B) and protein kinase B (Akt) signalling pathways inhibition and GSTP1 (Glutathione S-transferase P), RASSF1A (Ras association domain-containing protein 1), EPH2 (ephrin type-A receptor 2), BRCA1 promoter (Breast cancer susceptibility gene 1), methylation (Vardi *et al*., 2010).

Curcumin is a polyphenol extracted from *Curcuma longa* rhizomes and is recognized for its anti-tumor and chemopreventive effects. This compound acts on the major pathogenic pathways for blood cancer, activates the tumor suppressor gene - p53 and represses NF-*κ*appa B, exhibiting its anticancer properties (McCubrey *et al*., 2012; Sidhar *et al*., 2017; Marin *et al*., 2007).

Various natural carotenoids like, alpha- and beta-carotenes, lutein, zeaxanthin, lycopene, beta-cryptoxanthin, fucoxanthin, astaxanthin, capsanthin, phytoene, have the ability to reduce the oxidative stress by modulating ROS-producing enzymes (Nishino *et al.*, 2002; Tanaka *et al.*, 2012), to act on the expression of cell cycle

regulatory proteins in order to inhibit the cancer cell proliferation, or to inactivate the growth factor (Platelet-derived growth factor-PDGF, Vascular endothelial growth factor-VEGF, Insulin-like growth factor -IGF)-induced PI3K/AKT/PKB and Ras/RAF/MAPK signalling pathways (Seren *et al*., 2008; Ip and Wang, 2013; Sahin *et al.*, 2010; Trejo-Solís *et al.*, 2013; Sahin *et al*., 2017).

Overall, these bioactive compounds are promising as nutraceuticals in the alternative cancer therapy but their mechanism of action is complex and require integral studies of transcriptomics, nutrigenetics, proteomics and metabolomics.

Conclusions

Indubitably, nutrigenomics and nutrigenetics are sciences with a higher impact on nutrition area. Nowadays obesity, metabolic syndromes, type 2 diabetes mellitus or cancer with their plethora of clinical manifestations are the main concerns of society. The natural compounds are able to exhibit important antioxidant and antitumor properties by blocking specific enzymes or some checkpoints in the cell cycle, or by many others mechanisms.

The vision that nutrigenomics/nutrigenetics offers at this moment is promising and can be very well applied, perhaps, in the next 20 years.

Whole-genome sequencing, and the analysis of genetic expression profile will reveal for each person, its risk on illness developing, in the context of gene-nutrient association. It will be possible to access a personalized diet aiming to prevent diseases and to improve the quality of live.

References

Abdullah, M.M., Cyr, A., Lepine, M.C., Eck, P.K., Couture, P., Lamarche, B., et al. 2016. Common variants in cholesterol synthesis- and transport-related genes associate with circulating cholesterol responses to intakes of conventional dairy products in healthy individuals. *Journal of Nutrition*, **146**(5), 1008-1016.

Abdullah, M.M., Eck, P.K. Couture, P., Lamarche, B., Jones, J.H. 2018.The combination of single nucleotide polymorphisms rs6720173 (*ABCG5*), rs3808607 (*CYP7A1*), and rs760241 (*DHCR7*) is associated with differing serum cholesterol responses to dairy consumption. Brief Communication. *Applied Physiology, Nutrition, and Metabolism*, **43**(10), 1090-1093.

Acuña-Alonzo, V., Flores-Dorantes, T., Kruit, J.K., Villarreal-Molina, T., Arellano-Campos, O., Hünemeier, T., Moreno-Estrada, A., Ortiz-López, M.G., Villamil-Ramírez, H., León-Mimila, P., et al. 2010. A functional ABCA1 gene variant is associated with low HDL-cholesterol levels and shows evidence of positive selection in Native Americans. *Human Molecular Genetics*, **19**, 2877-2885.

Ali, K. M., Wonnerth, A., Huber, K., Wojta, J. 2012. Cardiovascular disease risk reduction by raising HDL cholesterol – current therapies and future opportunities. *British Journal of Pharmacology*, **167**, 1177–1194.

Arthur, J.S., Ley, S.C. 2013. Mitogen-activated protein kinases in innate immunity. *Nature Reviews Immunology*, **13**(9), 679–92.

Banerjee, S., Li, Y., Wang, Z., Sarkar, F.H. 2008. Multi-targeted therapy of cancer by genistein, *Cancer Letters*, **269**(2), 226–242.

Barish, G.D., Narkar, V.A., Evans, R.M. 2006. PPAR delta: A dagger in the heart of the metabolic syndrome. *Journal of Clinical Investigation*, **116**, 590–7.

Cameron, A.J., Shaw, J.E., Zimmet, P.Z. 2004. The metabolic syndrome: prevalence in worldwide populations. *Endocrinology and Metabolism Clinics of North America*, **33**, 351–375.

Cargnello, M., Roux, P.P. 2011. Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiology and Molecular Biology Reviews*, **75**(1), 50–83.

Chen, G., Wang, H., Zhang, X., and Yang, S. T. 2014. Nutraceuticals and functional foods in the management of hyperlipidemia. *Critical Reviews in Food Science and Nutrition*, **54**, 1180–1201.

Chowdhury, R., Warnakula, S., Kunutsor, S., Crowe, F., Ward, H.A., Johnson, L., Franco, O.H., Butterworth, A.S., Forouhi, N.G., Thompson, S.G., Khaw, K.T., Mozaffarian, D., Danesh, J., Angelantonio, E. Di. 2014. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis, *Annals of Internal Medicine*, **160**, 398–406.

Claussnitzer, M., Dankel, S. N., Kim, K.-H., Quon, G., Meuleman, W., Haugen, C., et al. 2015. FTO obesity variant circuitry and adipocyte browning in humans. *The New England Journal of Medicine*, **373**(10), 895–907.

Cook, L.S., Goldoft, M., Schwartz, S.M.,Weiss, N.S. 1999. Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. *The Journal of Urology*, **161**(1), 152–55.

Coppedè, F. 2015. The genetics of folate metabolism and maternal risk of birth of a child with Down syndrome and associated congenital heart defects. *Frontiers in Genetics*, **6**, 223.

de Pablo, M.A. and Alvarez de Cienfuegos G. 2000. Modulatory effects of dietary lipids on immune system functions. *Immunology and Cell Biology*, **78**, 31–39.

de Toro-Martín, J., Arsenault, B. J., Després, J. P., Vohl, M. C. 2017. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. *Nutrients*, ***9***(8), 913.

Dhar, S., Hicks, C., Levenson, A.S. 2011. Resveratrol and prostate cancer: promising role for microRNAs. *Molecular Nutrition & Food Research*, **55**, 1219–1229.

Do, R., Xie, C., Zhang, X., Männistö, S., Harald, K., et al. 2011. The Effect of chromosome 9p21 variants on cardiovascular disease may be modified by dietary intake: Evidence from a Case/Control and a Prospective Study. *PLOS Medicine*, **8**(10), e1001106.

Dong, J., Ping, Y, Wang, Y., Zhang, Y. 2018. The roles of endothelial nitric oxide synthase gene polymorphisms in diabetes mellitus and its associated vascular complications: a systematic review and meta-analysis. *Endocrine*, **62**(2), 412-422.

Du, Q., Hu, B., An, H.M., Shen, K.P., Xu, L., Deng, S., Wei, M.M. 2013. Synergistic anticancer effects of curcumin and resveratrol in Hepa1-6 hepatocellular carcinoma cells, *Oncology Reports*, **29**(5), 1851–1858.

Desai, M., Chauhan, J.B., 2016b. Analysis of MTHFR C677T and A1298C polymorphism in Down syndrome and other intellectually disabled children. *International Journal of Recent Scientific Research*, **7**, 14908–14913.

Donahue, S.M., Rifas-Shiman, S.L., Gold, D.R., Jouni, Z.E., Gillman, M.W., Oken, E. 2011. Prenatal fatty acid status and child adiposity at age 3 years: Results from a US pregnancy cohort. *The American Journal of Clinical Nutrition*, **93**, 780–788.

Farràs, M., Castañer, O., Martín-Peláez, S., Hernáez,Á., Schröder, H., Subirana, I., et al. 2015. Complementary phenol-enriched olive oil improves HDL characteristics in Hypercholesterolemic subjects. A randomized, double-blind, crossover, controlled trial. The VOHF study. *Molecular Nutrition & Food Research*, **59**, 1758–1770.

Fohr, I.P., Prinz-Langenohl, R., Brönstrup, A., Bohlmann, A.M., Nau, H., Berthold, H.K., Pietrzik, K. 2002. 5,10-Methylenetetrahydrofolate reductase genotype determines the plasma homocysteine-lowering effect of supplementation with 5-methyltetrahydrofolate or folic acid in healthy young women. *The American Journal of Clinical Nutrition*, **75**(2), 275-82.

Frayling, T. M., Timpson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M., Lindgren, C. M., et al. 2007. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*, **316**(5826), 889–894.

German, J. B., Zivkovic, A. M., Dallas, D. C., Smilowitz, J. T. 2011. Nutrigenomics and personalized diets: What will they mean for food? *Annual review of food science and technology*, **2**, 97-123.

Goyal, R., Goyal, D., Leitzke, A., Gheorghe, C.P., Longo, L.D. 2010. Brain renin-angiotensin system: Fetal epigenetic programming by maternal protein restriction during pregnancy. *Reproductive Sciences (Thousand Oaks, CA)*, **17**(3), 227–38.

Gordon, T., Castelli, W.P., Hjortland, M.C, Kannel, W.B., Dawber, T.R. 1977. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *The American Journal of Medicine*, **62**, 707–714.

Harris, W. S., von Schacky, C., Park, Y. 2013. Standardizing methods for assessing omega-3 fatty acid biostatus. In the omega-3 fatty acid deficiency syndrome: opportunities for disease prevention. *Nova Science Publishers*, Inc. 385-398.

Harris, W. S. 2018. The omega-6:omega-3 ratio: a critical appraisal and possible successor. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, **132**, 34–40.

Haslam, D.E., McKeown, N.M., Herman, M.A., Lichtenstein, A.H. Dashti, H.S. 2018. Interactions between genetics and sugar-sweetened beverage consumption on health outcomes: A Review of Gene–Diet Interaction Studies. *Frontiers in Endocrinology*, **8**, 368.

Hernáez, A., Farràs, M., and Fitó, M. 2016. Olive oil phenolic compounds and high-density lipoprotein function. *Current Opinion in Lipidology*, **27**, 47–53.

Heneka, M.T., Landreth, G.E. 2007. PPARs in the brain. *Biochimica et Biophysica Acta*, **1771**, 1031–45.

Hindy, G., Ericson, U., Hamrefors, V., Drake, I., Wirfält, E., Melander, O., Orho-Melander, M. 2014. The chromosome 9p21 variant interacts with vegetable and wine intake to influence the risk of cardiovascular disease: A population based cohort study. *BMC Medical Genetics*, **15**, 1220.

Imai, K., Suga, K., and Nakachi, K. 1997.Cancer-preventive effects of drinking green tea among a Japanese population. *Preventive Medicine*, **26**(6), 769–75.

Ip, B.C., Wang, X.D. 2013. Non-alcoholic steatohepatitis and hepatocellular carcinoma: implications for lycopene intervention. *Nutrients*, **6**(1), 124-162.

Kang, J.X. 2003. The importance of omega-6/omega-3 fatty acid ratio in cell function. The gene transfer of omega-3 fatty acid desaturase. In *omega-6/omega-3 essential fatty acid ratio: the scientific evidence*; Simopoulos, A.P., Cleland, L.G., *World Review of Nutrition and Dietetics*, Basel, Karger, **92**, 23-36.

Kaufman, P. B., Duke, J. A., Brielmann, H., Boik, J. Hoyt, J. E. 1997. A comparative survey of leguminous plants as sources of the isoflavones, genistein and daidzein: implications for human nutrition and health, *The Journal of Alternative and Complementary Medicine*, **3**(1), 7–12.

Ke, T., Dorajoo, R., Han, Y., Khor, C.C., M.R. van Dam, Yuan, J.M., Koh, W.P., Liu, J.,Teo, Y.Y., Goh, D.Y.T., Tai, E. S., Wong, T.Y., Cheng C.Y., Friedlander, Y., Heng, C.K. 2016. Interaction between peroxisome proliferator activated receptor δ and epithelial membrane protein 2 polymorphisms influences HDL-C levels in the chinese population. *Annals of Human Genetics*, **80**, 282–293.

Kim, M., Kim M., Huang, L., Jee, S.J., Lee, J.H. 2018. Genetic risk score of common genetic variants for impaired fasting glucose and newly diagnosed type 2 diabetes influences oxidative stress. *Scientific Reports*, **8**, 7828.

Kim, M., Kim, M., Yoo, H. J., Bang, Y. J., Lee, S.-H., Lee, J. H. 2018. *PPARD* rs7770619 polymorphism in a Korean population: Association with plasma malondialdehyde and impaired fasting glucose or newly diagnosed type 2 diabetes. *Diabetes and Vascular Disease Research*, **15**(4), 360–363.

Kim, M., Kim, M., Yoo, H. J., Bang, Y. J., Lee, S.-H., Lee, J. H. 2018. APOA5 variants are associated with decreased adiponectin levels and increased arterial stiffness in subjects with low HDL-cholesterol levels. *Clinical Genetics*, **94(**5), 438-444.

Kirwan, L., Walsh, M.C., Celis-Morales, C., Marsaux, C.F.M., Livingstone, K.M., Navas-Carretero, S., Fallaize, R., O'Donovan, C.B., Woolhead, C., Forster, H., et al. 2016. Phenotypic factors influencing the variation in response of circulating cholesterol level to personalised dietary advice in the Food4Me study. *British Journal of Nutrition*, **116**, 2011–2019.

Kohlmeier, M., De Caterina, R., Ferguson, L.R. *et al.* 2016. Guide and position of the international society of nutrigenetics/ nutrigenomics on personalized nutrition: part 2 – ethics, challenges and endeavors of precision nutrition. *Journal of Nutrigenetics and Nutrigenomics*, **9(1**), 28–46.

Kromhout, D., de Goede, J. Update on cardiometabolic health effects of ω-3 fatty acids. 2014. *Current Opinion in Lipidology*, **25**, 85–90.

Kruger, M.C., Coetzee, M., Haag, M., Weiler, H. 2010. Long-chain polyunsaturated fatty acids: selected mechanisms of action on bone. *Progress in Lipid Research*, **49**, 438–449.

Jung, D., Cao, S., Liu, M., Park, S. 2018. A meta-analysis of the associations between the ATP-binding cassette transporter ABCA1 R219K (rs2230806) polymorphism and the risk of type 2 diabetes in asians. *Hormone and Metabolic Research*, **50**(4), 308-316.

Lye, S-H., Chahil, J.K., Bagali, P., Alex, L., Vadivelu, J, et al. 2013. Genetic polymorphisms in LDLR, APOB, PCSK9 and other lipid related genes associated with familial hypercholesterolemia in Malaysia. *PLoS ONE*, **8(**4), e60729.

Ma, X.-y., Liu, J. P, Song, Z.Y. 2011. Associations of the ATP-binding cassette transporter A1 R219K polymorphism with HDL-C level and coronary artery disease risk: a meta-analysis. *Atherosclerosis*, **215**(2), 428-34.

Marin, Y.E., Wall, B.A., Wang, S., Namkoong, J., Martino, J.J., Suh, J., Lee, H.J., Rabson, A.B., Yang, C.S., Chen, S., Ryu, J.H. 2007. Curcumin downregulates the constitutive activity of NF-kappaB and induces apoptosis in novel mouse melanoma cells. *Melanoma Research*, **17**(5), 274–283.

Marques, L.R., Diniz, T.A., Antunes, B.M., Rossi, F.E., Caperuto, E.C., Lira, F.S. and Gonçalves, D.C. 2018. Reverse cholesterol transport: molecular mechanisms and the non-medical approach to enhance HDL cholesterol. *Frontiers in Physiology*, **9**, 526.

Mansi Desai, J.B. Chauhan. 2018. Computational analysis for the determination of deleterious nsSNPs in human MTHFR gene. *Computational Biology and Chemistry*, **74**, 20–30.

McCubrey, J.A., Steelman, L.S., Chappell, W.H., Abrams, S.L., Montalto, G., Cervello, M., Nicoletti, F., Fagone, P., Malaponte, G., Mazzarino, M.C., Candido, S., Libra, M., Basecke, J., Mijatovic, S., *et al.* 2012. Mutations and deregulation of Ras/Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR cascades which alter therapy response, *Oncotarget*, **3(**9), 954–987.

Meeran, S.M., Patel, S.N., Chan, T-H., Tollefsbol, T. O. 2011. A Novel Prodrug of Epigallocatechin-3-gallate: Differential epigenetic *hTERT* repression in human breast cancer cells. *Cancer Prevention Research*, **4**(8), 1243-1254.

Mensink, R.P., Zock, P.L., Kester, A.D., Katan, M.B. 2003. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *The American Journal of Clinical Nutrition*, **77**, 1146–1155.

Moreno, S., Farioli-Vecchioli, S., Cerù, MP. 2004. Immuno localization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat *CNS. Neuroscience*, **123**, 131–45.

Nicholas, L.M., Rattanatray, L., MacLaughlin, S.M., Ozanne, S.E., Kleemann, D.O., Walker, S.K., et al. 2013. Differential effects of maternal obesity and weight loss in the periconceptional period on the epigenetic regulation of hepatic insulin-signaling pathways in the offspring. *The FASEB Journal*, **27**(9), 3786–96.

Nielsen, D**.**E**.,** El-Sohemy, A. 2012. A randomized trial of genetic information for personalized nutrition. *Genes and Nutrition*, **7**(4), 559–566.

Nishino, H., Murakosh, M., Ii, T., Takemura, M., Kuchide, M., Kanazawa, M., Mou, XY., Wada, S., Masuda, M., Ohsaka, Y., Yogosawa, S., Satomi, Y., Jinno, K .2002. Carotenoids in cancer chemoprevention. *Cancer and Metastasis Reviews*, **21**(3-4), 257-64.

Nojima, M., Iwasaki, M., Kasuga, Y., Yokoyama, S., Onuma, H., Nishimura, H., Kusama, R., Yoshida, T. and Tsugane, S. 2018. Correlation between global methylation level of peripheral blood leukocytes and serum C reactive protein level modified by MTHFR polymorphism: a cross-sectional study. *BMC Cancer*, **18**, 184.

Olsen, N.J., Ängquist, L., Larsen, S.C., Linneberg, A., Skaaby, T., Husemoen, L.L.N., et al. 2016. Interactions between genetic variants associated with adiposity traits and soft drinks in relation to longitudinal changes in body weight and waist circumference. *The American Journal of Clinical Nutrition*, **104**, 816–26.

Omene, C., Kalac, M., Wu, J., Marchi, E., Frenkel, K., O'Connor, O.A. 2013. Propolis and its active component, caffeic acid phenethyl ester (CAPE), modulate breast cancer therapeutic targets via an epigenetically mediated mechanism of action. *Journal of Cancer Science and Therapy*, **5**(10), 334–342.

Ono, H., Iwasaki, M., Kuchiba, A., Kasuga, Y., Yokoyama, S., Onuma, H., et al. 2012. Association of dietary and genetic factors related to one-carbon metabolism with global methylation level of leukocyte DNA. *Cancer Science*, **103**, 2159–64.

Onuma, H., Tabara, Y., Kawamoto, R., Shimizu, I., Kawamura, R., Takata, Y., Nishida, W., Ohashi, J., Miki, T., Kohara, K., Makino, H., Osawa, H. 2010. The GCKR rs780094 polymorphism is associated with susceptibility of type 2 diabetes, reduced fasting plasma glucose levels, increased triglycerides levels and lower HOMA-IR in Japanese population. *Journal of Human Genetics*, **55**(9), 600-4.

Phillips, C.M., Goumidi, L., Bertrais, S., Field, M.R., Cupples, L.A., et al. 2010. Gene nutrient interactions with dietary fat modulate the association between genetic variation of the ACSL1 gene and metabolic syndrome. *The Journal of Lipid Research*, **51**, 1793–1800.

Raimondi, S., Johansson, H., Maisonneuve, P., Gandini, S. 2009. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. *Carcinogenesis*, **30**, 1170–1180.

Raj, R., Bhatti, J.S., Sanjay, Bhadada K., Ramteke, P.W. 2017. Association of polymorphisms of peroxisome proliferator activated receptors in early and late onset of type 2 diabetes mellitus. *Diabetes Metabolic Syndrome: Clinical Research and Reviews* **11S**, S287–S293.

Ramayo-Caldas, Y., Mach, N., Esteve-Codina, A., Corominas, J., Castello, A., Ballester, M., Estelle, J., Ibanez-Escriche, N., Fernandez, A.I., Perez-Enciso, M., Folch, J.M. 2012. Liver transcriptome profile in pigs with extreme phenotypes of intramuscular fatty acid composition. *BMC Genome*, **13**, 547.

Rondanelli, M., Giacosa, A., Morazzoni, P., Guido, D., Grassi, M., Morandi, G., et al. 2016. Mediterr Asian diet products that could raise HDL-cholesterol: a systematic review. *BioMed Research International*, **2025687**, 1-15.

Rudkowska, I., Dewailly, E., Hegele, R.A., Boiteau,V., Dubé-Linteau, A., Abdous, B., Giguere, Y., Chateau-Degat, M. L., Vohl, M.C. 2013. Gene-diet interactions on plasma lipid levels in the Inuit population. *British Journal of Nutrition*, **109**(5), 953-61.

Sahin, K., Tuzcu, M., Sahin, N., Ali, S., Kucuk, O. 2010. Nrf2/HO-1 signaling pathway may be the prime target for chemoprevention of cisplatin-induced nephrotoxicity by lycopene. *Food and Chemical Toxicology*, **48**(10), 2670-2674.

Sahin, K., Ali, S., Sahin, N., Orhan, C., Kucuk, O. 2017. Chapter 5. Lycopene: multitargeted applications in cancer therapy. Natural products and cancer drug discovery. *InTechOpen*, 79-108.

Saccucci, P., Compagnone, E., Verrotti, A., Galasso, C., Curatolo, P. 2008. Lack of association between MTHFR C677T and MTHFR A1298C genetic polymorphism and mental retardation. *Nutritional Neuroscience*, **11**, 241–242.

Scacchi, R., Pintro, A., Rickards O., Pacella, A., Cannella, C., De Stefano, G.F., et al. 2007. An analysis of peroxisome proliferator-activated receptor gamma (PPAR-γ2) Pro12Ala polymorphism distribution and prevalence of type 2 diabetes mellitus (T2DM) in world populations in relation to dietary habits. *Nutrition, Metabolism and Cardiovascular Diseases*, **17**, 632–41.

Seren, S., Lieberman, R., Bayraktar, U.D., Heath, E., Sahin, K., Andic, F., Kucuk, O. 2008. Lycopene in cancer prevention and treatment. *American Journal of Therapeutics*, **15**(1), 66-81.

Sharma P., Dwivedi S. 2017. Nutrigenomics and Nutrigenetics: New insight in disease prevention and cure. *Indian Journal of Clinical Biochemistry*, **32(4)**, 371–373.

Shi, J., Hed, W., Wangb, Y., Hua, J. 2018. Tagging functional polymorphism in 3' untranslated region of methylene tetrahydrofolate reductase and risk of ischemic stroke. *Cellular Physiology and Biochemistry*, **46**, 1019-1026.

Sidhar, H., Giri, R.K. 2017. Induction of Bex genes by curcumin is associated with apoptosis and activation of p53 in N2a neuroblastoma cells. *Scientific Report*s, **7**, 41420.

Simopoulos, A.P. 2003. Evolutionary aspects of diet and essential fatty acids. In *Fatty Acids and Lipids—New Findings*, Simopoulos, A.P., Cleland, L.G., Eds. Karger: Basel, **92**, 23–36, Switzerland.

Simopoulos, A.P. 2008. The importance of the omega-6/omega-3 Fatty Acid ratio in cardiovascular disease and other chronic diseases. *Experimental Biology and Medicine* **233**, 674–688.

Simopoulos, A.P. 2010. Nutrigenetics/Nutrigenomics. *Annual Review of Public Health*, **31**(1), 53–68.

Simopoulos, A.P. 2013. Dietary Omega-3 Fatty Acid Deficiency and High Fructose Intake in the Development of Metabolic Syndrome, Brain Metabolic Abnormalities, and Non-Alcoholic Fatty Liver Disease. *Nutrients*, **5**, 2901–2923.

Simopoulos, A.P. 2016. An increase in the omega-6/omega-3 fatty acid ratio increases the risk for obesity. *Nutrients*, **8**, 128.

Siri-Tarino, P. W. 2011. Effects of diet on high-density lipoprotein cholesterol. *Current Atherosclerosis Reports*, **13**, 453–460.

Stover, P. J. 2004. Nutritional genomics. *Physiological Genomics*, **16**(2), 161-5.

Sonestedt, E., Hellstrand, S., Schulz, C-A, Wallström, P., Drake, I., Ericson, U., et al. 2015. The association between carbohydrate-rich foods and risk of cardiovascular disease is not modified by genetic susceptibility to dyslipidemia as determined by 80 validated variants. *PLoS One*, ***10***(4), e0126104.

Szostak, A., Ogłuszka, M., te Pas, M. F. W., Poławska, E, Urbański, P., Juszczuk-Kubiak, E., Blicharski, T., Pareek, C.S.,. Dunkelberger, J.R, Horbańczuk, J.O., Pierzchała, M. 2016. Effect of a diet enriched with omega-6 and omega-3 fatty acids on the pig liver transcriptome. *Genes & Nutrition*, **11**, 9.

Takeuchi, F., Isono, M., Nabika, T., Katsuya, T., Sugiyama, T., Yamaguchi, S., et al. 2011. Confirmation of ALDH2 as a major locus of drinking behavior and of its variants regulating multiple metabolic phenotypes in a Japanese population. *Circulation Journal*, **75**(4), 911–8.

Tanaka, T., Shnimizu, M., Moriwaki, H. 2012. Cancer chemoprevention by carotenoids. *Molecules*, **17**(3), 3202-42.

Tili, E., Michaille, J.J., Alder, H., Volinia, S., Delmas, D., Latruffe, N., Croce, C.M. 2010. Resveratrol modulates the levels of microRNAs targeting genes encoding tumor-suppressors and effectors of TGFβ in signaling pathway in SW480 cells. *Biochemical Pharmacology*, **80**, 2057–2065.

Tyagi, S., Gupta, P., Singh Saini, A., Kaushal, C., Sharma, S. 2011. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. *Journal of Advanced Pharmaceutical Technology & Research*, **2**(4), 236–240.

Torrens, C., Brawley, L., Anthony, F.W., Dance, C.S., Dunn, R., Jackson, A.A., et al. 2006. Folate supplementation during pregnancy improves offspring cardiovascular dysfunction induced by protein restriction. *Hypertension*, **47**(5), 982–7.

Trejo-Solís, C., Pedraza-Chaverrí, J., Torres-Ramos, M., Jiménez-Farfán, D., Cruz Salgado, A., Serrano-García, N., Osorio-Ric,o L., Sotelo, J. 2013. Multiple molecular and cellular mechanisms of action of lycopene in cancer inhibition. *Evidence-Based Complementary and Alternative Medicine*, 2013, 705121.

Vamecq, J., Cherkaoui-Malki M., Andreoletti, P., Latruffe, N. 2014. The human peroxisome in health and disease: The story of an oddity becoming a vital organelle. *Biochimie*, **98**, 4-15.

Vardi, A., Bosviel, R., Rabiau, N., Adjakly, M., Satih, S., Dechelotte, P., Boiteux, J.P., Fontana, L., Bignon, Y.J., Guy, L., Bernard-Gallon, D.J. 2010. Soy phytoestrogens modify DNA methylation of *GSTP1*, *RASSF1A*, *EPH2* and *BRCA1* promoter in prostate cancer cells, In Vivo, **24**(4), 393–400.

Wang, Y., Zhang, Y., Zhang, J., Tang, X., Qian, Y., Gao, P., et al. 2013. Association of a functional single-nucleotide polymorphism in the ALDH2 gene with essential hypertension depends on drinking behavior in a Chinese Han population. *Journal of Human Hypertension*, **27**(3), 181–186.

Weng, C.J., Yen, G.C. 2012. Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives, *Cancer Treatment Reviews*, **38**(1), 76–87.

Wymann, M.P., Schneiter, R. 2008. Lipid signalling in disease. *Nature Reviews Molecular Cell Biology*, **9**, 162–176.

Wubetu, G.Y., Shimada, M., Morine, Y., Ikemoto, T., Ishikawa, D., Iwahashi, S., Yamada, S., Saito, Y., Arakawa, Y., Imura, S., 2016. Epigallocatechin gallate hinders human hepatoma and colon cancer sphere formation. *Journal of Gastroenterology and Hepatology*, **31**(1), 256–264.

Zhuang, P., Wang, W., Wang, J., Zhang, Y., Jiao, J. 2018. Polyunsaturated fatty acids intake, omega-6/omega-3 ratio and mortality: Findings from two independent nationwide cohorts. *Clinical Nutrition*, 1-8.