

## REVIEW ARTICLE

# Potential of Nutraceutical in Preventing the Risk of Cancer and Metabolic Syndrome: From the Perspective of Nutritional Genomics

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**Abstract:** Cancer and metabolic syndrome (MetS) are associated with genetic mutation and often seen as the results of altered metabolic signals. Several nutraceuticals have been found to be effective in treating these diseases in clinical practice through the modulation of biochemical and clinical endpoints associated with the pathogenesis of cancer and MetS. In line with the availability of multiple interventions that could counteract the metabolic changes, there is mounting evidence for nutraceuticals as potential complementary medicine for these diseases on the foundation of their multi-factorial nature. Although cancer and MetS are the major contributors to deaths globally, the therapeutic effects of nutraceuticals and the role of nutritional genetics and nutritional genomics in the treatment of these diseases have not yet been explored in-depth. In recent years, many studies revealed that certain compounds are able to halt the progression of cancer and MetS and subsequently improve individual health through the regulation of metabolic gene expression. In this review, we examine the relationship of nutraceutical, nutritional genetics, and nutritional genomics in the context of personalized medicine. The discrepancies in response to bioactive food components due to inter-individual variabilities in genetics, epigenetics, transcriptomics, proteomics, and metabolomics are also discussed.

**Keywords:** Nutraceutical, Nutritional genetics, Cancer, Metabolic syndrome, Personalized medicine

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## 1. Introduction

A selection of nutraceuticals has received much attention for their potential effect against life-threatening cancer and metabolic syndrome (MetS). Cancer is a leading cause of mortality, causing the death of one in eight adults worldwide<sup>[1]</sup>. Previous studies revealed that roughly 30–40% of all cancers are influenced by diet, histological type of cancer, tumor markers, molecular subtype, and diet-specific components<sup>[1]</sup>. To transform from a normal cell into a cancerous phenotype, the cell will need to go through initiation, progression, and advancement due to the mutations or altered expression of particular genes<sup>[2]</sup>.

Several compounds obtained from plants, namely isoflavones, curcumin, green tea polyphenols, ferulic acid, resveratrol, lycopene, etc., have shown healing activities<sup>[2]</sup>.

Most importantly, these compounds are reported to have the ability to quash the process of carcinogenesis and metabolic abnormalities<sup>[2,3]</sup>. These agents have also been shown to delay cancer and MetS development by mitigating the corresponding signaling pathways<sup>[3,4]</sup>. The modification in the nutritional or biochemical composition of the food can affect disease progression by changing the expression of particular genes or function of their protein products in a vastly complex process<sup>[5]</sup>. Conventionally, nutrition is considered an integral part of health, but the human population's genetic diversity and food habits may develop an individual risk factor<sup>[5]</sup>. Overeating and low dietary inclusion of nutraceuticals may play a role in the development of cancer- and MetS-related features<sup>[5]</sup>. These features include central obesity, dyslipidemia, hypertension, insulin resistance, and primary metabolism alteration<sup>[5,6]</sup>. Nutraceuticals, such as antioxidants, flavonoids, glycosinolates, phytoestrogen, dietary fibers, and carotenoids, are found to improve health issues<sup>[6-9]</sup>.

Nutritional genetics is the study concerning the molecular relationship between nutrients and genes in the body and the response of nutrients to genetic differences<sup>[10]</sup>. Nutritional genetics focuses on the understanding of the interaction of nutritional and genetic factors in relation to disease etiology and the evaluation of genetic and epigenetic alterations in response to a particular dietary component that leading to an alteration in the disease status<sup>[11,12]</sup>. In addition, the main goal of nutritional genetics is to look into the impact of genetic variation, particularly single nucleotide polymorphism (SNP), on an individual's reaction to dietary intake and how genetic variation influences an individual's metabolic state<sup>[13,14]</sup>. Of note, a SNP may potentially affect the changes of transcriptomics, metabolomics, and proteomics<sup>[15]</sup>. At present, a better understanding of nutritional genetics allows us to effectively select suitable nutraceuticals as complementary and alternative medicine<sup>[15,16]</sup>. Caffeine, a ubiquitous nutraceutical, is a good example that how nutritional genetics knowledge is utilized. Caffeine users vary in responses due to the genetic polymorphism in cytochrome P450 1A2 (*CYP1A2*) gene that encodes an enzyme called the CYP1A2<sup>[17]</sup>. The enzyme, which is synthesized in the liver, demethylates caffeine, and the enzyme encoded from the *CYP1A2* gene with polymorphic variants may demethylate caffeine more quickly<sup>[17,18]</sup>.

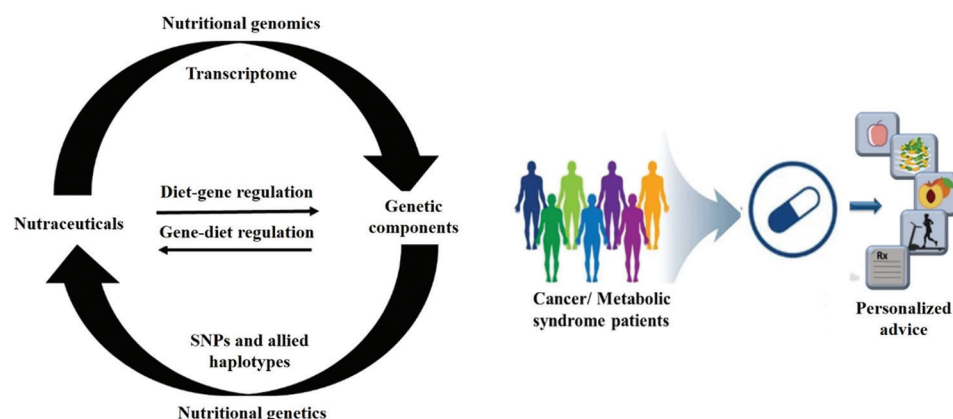
Nutritional genomics is concerned with how bioactive chemicals in food and supplements alter an individual's genetic makeup and their effects on proteome and metabolome<sup>[6,19]</sup>. The foremost objective of nutritional genomics is to explore the impact of diet and nutrition on gene expression, primarily through high-throughput assays for epigenomics (e.g., histone methylation), transcriptomics (e.g., RNA transcription), proteomics (e.g., protein synthesis), and metabolomics (e.g., metabolite synthesis)<sup>[20]</sup>. For instance, the impact of the ingestion of soy isoflavone, a type of nutraceutical, on

various pathways associated with energy metabolism can be explained from the viewpoints of nutritional genomics<sup>[21,22]</sup>. Personal health conditions and disease susceptibility may be recognized by defining metabolic response and gene expression. Thus, under the broad definition of nutritional genomics, genotypes and the environment play a role in the design of personalized diet for individuals and disease prevention<sup>[21,22]</sup>.

In this review, we propose an idea that the relationship between nutraceuticals, nutritional genetics, and nutritional genomics can be expressed as the pillars of complementary medicine where the area of nutritional genetics focuses on the identification of SNPs and allied haplotypes, while the area of nutritional genomics focuses on the determination of expression of genes related to diet through high-throughput omics technology. These principles work together in a way that the SNPs identified through the nutritional genetics approach can be fed into the nutritional genomics approach to unravel the candidate genes, thereby laying the basis for constructing a personalized diet for reducing the risks for diseases (**Figure 1**). There is an interacting two-way rapport between nutrition and human genome. The interrelationship of gene expression and metabolic response presumably plays a role in an individual's health condition and vulnerability to disease<sup>[23]</sup>. It may also help understand how nutrients can impinge on the metabolic pathways and how these regulations can be inhibited at the beginning phase of diet-related diseases<sup>[24]</sup>. By understanding the mechanisms of interactions between nutrients and genes through nutritional genomics approach, we may be able to determine the risk for particular diseases.

## 2. Influence of nutraceuticals and dietary components on cancer

Researchers worldwide have made a variety of approaches in the quest for fighting against cancers for several decades. However, cancer remains the second most common cause of death globally. Recently, dietary chemopreventive agents, especially bioactive constituents, and their application in reducing the effect of mutation have received much attention in cancer research. Many functional foods derived from plants, animals, or microbial sources are good candidates for cancer treatment. Nutraceuticals have noticeable anti-cancer effects that are executed in different mechanisms, including anti-metastatic activity, induction of apoptosis, and anti-proliferative activity. At present, the information about the remedial effects of sole compounds and combined nutraceuticals on cancer hindrance is growing. It has been reported that the biological effects of health-promoting foods can be well elucidated by observing synergistic impacts of the mixtures of bioactive compounds instead of the single constituent<sup>[25]</sup>. Epigallocatechin-3-gallate (EGCG), a type of polyphenol from green tea, has been found to exhibit anti-tumor and other essential activities, such as anti-metastatic activity<sup>[26]</sup>. EGCG is effective in



**Figure 1.** Future approaches in personalized medicine involving nutritional genomics and nutritional genetics.

inhibiting tumor invasion and angiogenesis, which are the processes happening at the onset of tumor development<sup>[26]</sup>. EGCG also suppresses melanoma cell expansion and metastasis by regulating activities related to tumor necrosis factor receptor-associated factor 6 (TRAF6), which is an adaptor protein that conciliates protein-protein interactions and is overexpressed in melanoma<sup>[2]</sup>. Other compounds from green tea were also found to be effective in inhibiting tumor metastases. For example, rhamnogalacturonan-II-type polysaccharide, a mature tea leave-based compound, can activate the immune system by enhancing activities of macrophages and natural killer (NK) cells<sup>[27]</sup>.

Green tea acts as a functional food, containing bioactive compounds such as catechins, epicatechin, and epigallocatechin that can help prevent liver and prostate cancer<sup>[28,29]</sup>. Vitamins, which are rich in nutraceutical properties, can prevent different types of cancer by regulating genes and mechanisms<sup>[30]</sup>. For example, Vitamin A is effective against glioma, lung, and colorectal cancers; Vitamin C is effective against solid tumors and hematological malignancies; Vitamin D is effective against colorectal, breast, prostate, and pancreatic cancers; Vitamin E is effective against prostate, colorectal, and breast cancer; and folic acid is effective against gastric colorectal, breast, and pancreatic cancer<sup>[30-33]</sup>. Selenium is an indispensable nutrient with many anti-cancer qualities, as disclosed in clinical and preclinical studies<sup>[34,35]</sup>. However, not all forms of selenium are efficient in reducing cancer risk according to the results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies trial. For instance, supplementation with selenomethionine did not prevent prostate cancer development<sup>[34,35]</sup>. Another critical nutrient is dietary folate which may be linked to carcinogenesis, more precisely, colorectal and pancreatic cancers when it is in deficiency. Folate is an active agent in maintaining DNA integrity through repairing, and reducing dietary levels may result in genomic instability through epigenetic mechanisms<sup>[36]</sup>. Intake of a diet with high calories and fats may also contribute to breast cancer, and salty food may be

linked to stomach cancer<sup>[37]</sup>. The results after administering both types of diet (high calories and fats) showed that there is an increase of metastasis, while the high-carbohydrate diet instigated enlargement in primary tumors<sup>[38]</sup>. In another study, it was found that a diet with low whole grains is a critical factor of carcinogenesis<sup>[39]</sup>.

Leafy vegetables and their bioactive constituents can control DNA damaging factors in cancer cells. DNA transcription in malignant tumors can be regulated by omega-3 fatty acids. Specific dietary components can decrease the probability of malignant transformation; in particular, omega-3 fatty acids have been found to reduce the risk for prostate cancer<sup>[40,41]</sup>. Incorporating some phytochemicals in regular diet has been found to prevent cancer by suppressing the expression of oncogenes. For example, the nutraceuticals in the following display anti-cancer effects: Caffeine, theophylline from cacao, tea, and coffee; limonene (monoterpenes) from citrus fruits; allicin (organosulfides) from garlic; organosulfides, mainly isothiocyanates and sulforaphane, from broccoli; carotenoids from beta-carotene; lycopene from tomatoes; flavonoids such as EGCG from green tea, quercetin from black tea, and curcumin from turmeric; phenolic acids such as capsaicin from chili peppers and indole-3-carbinol (organosulfides) from cabbage; ellagic acid from blackberries and raspberries; Gallic acid from pomegranate; stilbenes such as pterostilbene from blueberries and grapes; resveratrol from almonds, blueberries, and grapes; and isoflavones such as daidzein and genistein from soy<sup>[42-46]</sup>. Several studies suggested an inverse association between coffee drinking and pancreatic cancer risk, and coffee consumption was strongly correlated with reducing the risk for pancreatic cancer in men, while a similar association was not observed among women<sup>[47,48]</sup>. The intake of coffee rather than black tea had a protective effect on premenopausal breast cancer; however, the effect was not observed in postmenopausal breast cancer<sup>[47]</sup>. Ellagic acid (EA) can inhibit pancreatic cancer by suppressing cell proliferation, activation of caspase-3, and induction

of poly (ADP-ribosyl) polymerase cleavage. EA can also inhibit the expression of Bcl-2, cyclin D1, CDK2, and CDK6 while inducing the expression of the pro-apoptotic protein Bax in tumor tissues<sup>[48]</sup>.

A meta-analysis study revealed the protective effect of dietary flavonoids against ovarian cancer and reduced risk for ovarian cancer except<sup>[49]</sup>. A similar meta-analysis exposed that flavonols and flavones are correlated with a reduced breast cancer risk among postmenopausal women<sup>[50]</sup>. Dietary intake of total flavonoids, anthocyanidins, flavanones, and flavones effectively reduced esophageal cancer risk, as per a recent meta-analysis study<sup>[50,51]</sup>. A few meta-analyses suggest that soy isoflavone intake may be associated with reduced breast cancer risk in Asian populations and may be more protective in premenopausal women; however, the effect of dietary inclusion of on cancer growth is not apparent and not directly stated<sup>[52,53]</sup>. Furthermore, most studies that reported the benefits of soy consumption did not disclose the effects of its constituents on various stages of cancer and more specifically, metastasis. The inconsistency in anti-cancer properties of soy and other bioactive food components reflects the inter-individual variability. Many studies claimed that lessened the recurrence of breast cancer, thereby supporting soy isoflavones as an important research area in nutritional genetics or genomics. Furthermore, dietary polyphenols were found to have inhibitory effect on cancers, such as breast cancer and prostate cancer, through epigenetic mechanisms<sup>[54,55]</sup>.

Moreover, micronutrients (vitamins and trace minerals) and macronutrients are not only efficacious in preventing cancer but also in treating them, especially in terms of the hallmarks of cancer, ranging from limitless replicative potential to metastasis<sup>[56,57]</sup>. In this regard, diets containing flaxseeds have been shown to assist in breast cancer treatment through a mechanism by which a lignan from flaxseed transforms into a substance that binds to estrogen receptors and reduces cell growth<sup>[58]</sup>. Some specific examples of nutraceuticals and dietary components that influence cancer development are presented in **Table 1**.

### 3. Influence of nutraceuticals and dietary components on MetS

MetS is a syndrome that is characterized by elevated levels of sugar and blood pressure as well as abnormal levels of cholesterol or triglyceride. In MetS, the body's cells cannot take up glucose from the blood<sup>[74]</sup>. To be more specific, MetS is defined and classified as the presence of three or more of the following metabolic disorders: (i) central obesity (waist circumference  $\geq 102$  cm and  $\geq 88$  cm for men and women, respectively), (ii) dyslipidemia (high-density lipoproteins  $< 40$  mg/dL and  $< 50$  mg/dL for men and women respectively, or triglycerides  $\geq 150$  mg/dL), (iii) hypertension (systolic/diastolic blood pressure  $\geq 130/85$  mmHg), and (iv) insulin resistance (elevated fasting

blood glucose  $\geq 110$  mg/dL)<sup>[74]</sup>. MetS is considered when a set of traits, such as central obesity, insulin resistance, dyslipidemia, fatty liver, and hyperglycemia, leads to the development of type 2 diabetes and other cardiovascular diseases (CVD).

Even though MetS is a partly heritable disease, it can be potentially treated by nutraceuticals. Inflammation and oxidative stress may have an essential role in the pathogenesis of MetS<sup>[75]</sup>. The omega-3 fatty acids can significantly reduce MetS by reducing triglycerides and very low-density lipoprotein cholesterol and assuaging blood pressure and inflammatory markers. However, dietary patterns may be the key factor that may influence a genetic predisposition to MetS<sup>[76]</sup>. The dietary pattern based on the concept of personalized nutrition is a critical aspect in preventing the pathogenesis and progression of MetS. Dietary active ingredients may prevent or ameliorate metabolic disorders. A previous study observed that certain amino acids might influence pancreatic  $\beta$ -cell function from where insulin is secreted. The inclusion of branched-chain amino acids in dietary food may improve obesity and type 2 diabetes mellitus<sup>[77]</sup>. The study observed that polyunsaturated fatty acids might improve hypertensive, hyperlipidemia, and insulin sensitivity in individuals<sup>[78,79]</sup>. Epidemiological investigations found that habitual fish consumption (omega-3 fatty acid-containing fish) may reduce the frequency of type 2 diabetes mellitus. Conjugated linoleic acid (CLA)-rich diets may also improve insulin sensitivity in adipose tissue and liver. Dietary fiber intake from cereals and whole grains has an inverse relationship with body weight, diabetes, and CVD<sup>[80,81]</sup>. Dietary intake of flavonoids is inversely correlated with the risk for both diabetes mellitus and CVD<sup>[82]</sup>. Of note, it was found that the consumption of flavan-3-ols could lower the risk of coronary heart disease mortality<sup>[83]</sup>. A study on the European population observed that diet was significantly associated with overweight, obesity, and related comorbidities<sup>[84]</sup>.

Vitamin also plays an essential role in reducing MetS. For example, intake of Vitamin A, Vitamin C, Vitamin D, Vitamin E, and  $\beta$ -carotene improves glucose metabolism, prevents diabetes, and reduces the risk for CVD<sup>[85]</sup>. Dietary intake of magnesium and chromium may reduce the risk of CVD and type 2 diabetes mellitus<sup>[86]</sup>, respectively. Phytochemicals rich in polyphenols such as flavonoids (from cocoa, chocolate, grapes, black tea), resveratrol (from grapes, berries, and plums), isoflavones (from soy), chlorogenic acid (from apples, coffee beans, and carrots), ferulic acid, and  $\gamma$ -oryzanol (from fermented rice bran) have proven effects of reducing the risk of CVD and MetS<sup>[87]</sup>. On the other hand, supplementation of citrus polyphenol hesperidin to volunteers having MetS decreases the levels of circulating inflammatory biomarkers, such as C-reactive protein, serum amyloid A protein, and soluble E selectin, with simultaneous improvement of endothelial dysfunction<sup>[88]</sup>.

High-calorie diet intake may cause glucose and insulin



imbalance, leading to the development of lifestyle-related diseases such as diabetes and CVD<sup>[89]</sup>. However, regular consumption of resveratrol may decrease plasma glucose levels associated by improving insulin action and suppress cancer as well as lengthen lifespan<sup>[90]</sup>. The resveratrol is the parent molecule of the vinifera family and comes from various plants in response to stress. Resveratrol has been proven to exert biological effects even at shallow doses<sup>[91,92]</sup>. Resveratrol produces a SIRT1-dependent mechanism to improve cellular function and health in a mammalian cell. Duodenal SIRT1 and AMPK are compulsory for the insulin-sensitizing effect of resveratrol. Resveratrol activates duodenal-mucosal AMPK-SIRT1 pathway to lower hepatic glucose production and subsequently diminishes caloric intake and augments hepatic mitochondrial number<sup>[93]</sup>. Consumption of resveratrol and its related polyphenols can suppress cancers attributed to genomic instability. Resveratrol also regulates the NF- $\kappa$ B signaling pathway and NF- $\kappa$ B-dependent gene expression by inhibiting I $\kappa$ B kinase. Moreover, the inhibition of the expression of vascular cell adhesion molecules (VCAM) may elicit the development of atherosclerosis and hypertension<sup>[95,95]</sup>. The aptitude of resveratrol for precluding the harmful effects of excessive caloric intake and modulating known longevity pathways advocates that resveratrol might be the nutrient of choice for regulating energy balance, health, longevity, and lifestyle-related disease. Some nutraceuticals that can influence MetS are summarized in **Table 2**.

#### 4. Nutritional genomics and nutritional genetics approaches in cancer prevention and treatment

There are noticeable differences in cancer development in individuals who are on the same type of diet. This phenomenon can be explained by their genetic polymorphisms, which predominantly form the basis of nutritional genomics and nutritional genetics. Nutritional genomics and nutritional genetics may explain the association of nutrient intake with cancer pathogenesis and development in individuals with genetic variations<sup>[109]</sup>. Numerous nutraceuticals and dietary components can alter the genetic and epigenetic events<sup>[109,110]</sup>. Some genetic and epigenetic events include angiogenesis, proliferation, modulation of oncogene expression, and regulation of inflammation<sup>[109,110]</sup>. For example, anti-cancer nutraceuticals such as resveratrol regulate the NF- $\kappa$ B signaling pathway. Resveratrol also controls the NF- $\kappa$ B-dependent gene expression by inhibiting I $\kappa$ B kinase and TPA- and EGF-induced cell alteration and apoptosis<sup>[111,112]</sup>. Resveratrol has been found to reduce the viability of colorectal carcinoma cells through inhibition of adhesion kinase and focal adhesion<sup>[113]</sup>. It has also been reported that resveratrol may have beneficial effects if used as a chemopreventive agent for breast cancer<sup>[114,115]</sup>.

Glutathione peroxide gene polymorphism would be another good example in this regard<sup>[116]</sup>. It has been reported

that polymorphism at codon 198 of human glutathione peroxide gene that replaces proline (Pro) to leucine (Leu) is associated with an increased risk of lung cancer<sup>[117]</sup>. The individuals who possess the heterozygous genotype of Pro/Leu were found to have 80% greater risk of developing lung cancer, whereas the homozygous genotype of Leu/Leu was found to be associated with 130% greater risk. A plausible explanation is that in comparison to the proline allele, the leucine allele is less receptive to increased activity because of selenium supplementation<sup>[116]</sup>. A study also showed that genetic predisposition to prostate cancer is highly complex, probably involving numerous predisposition genes or genetic variations<sup>[117]</sup>. Sequencing of the human genome is capitalized for identifying disease-causing SNPs or genetic mutations in hereditary prostate cancer gene 1 (HPC1), androgen receptor, and Vitamin D receptor that are known to cause or correlate with cancers. Moreover, 50 – 90% of prostate cancer cases occur due to TMPRSS2-ETS gene family fusion; specifically, TMPRSS2-ERG or TMPRSS2-ETV1/4 promotes prostate cancer cell growth<sup>[117]</sup>. Certain types of cancers and metabolic disorders can be identified by genetic biomarkers summarized in **Table 3**.

#### 5. Nutritional genomics and nutritional genetics approaches in reducing MetS

Genetic susceptibility plays a pivotal role in the development of MetS that is influenced by both environmental and genetic factors; particularly, mutations and polymorphisms of the genes associated with several transcription factors may be the etiological factors of MetS<sup>[136]</sup>. Genome-Wide Association Study (GWAS) has so far identified more than 50 novel loci connected with ailments of glucose abnormalities and obesity<sup>[137]</sup>. The *transcription factor 7-like 2 (TCF7L2)* gene, whose protein regulates insulin secretion and sensitivity, is a major candidate gene for diabetes susceptibility<sup>[138]</sup>. Genes related to lipid metabolism, such as perilipin, apolipoprotein B, apolipoprotein E, fatty acid-binding proteins, and transcription factor 7-like 2, are associated with disturbed postprandial lipid metabolism, which is regarded as a feature of MetS. Besides, polymorphisms in tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and lymphotoxin exhibited an increased risk for central obesity, abnormalities of glucose levels, and MetS<sup>[139]</sup>. Other polymorphisms of genes, such as fat mass and obesity-associated protein (FTO) and acetyl-CoA carboxylase  $\beta$ , have also been reported to show an increased risk for MetS. The gene products of *APOA1* and *APOA5* are involved in regulating lipoprotein and triglycerides levels through modulating lipoprotein lipase activity, and the gene product of *APOE* mediates the binding of lipid complexes to cell receptors, and the expression of *APOA1*, *APOA5*, and *APOE* can be modulated through diet. Dietary supplementation with omega-3 polyunsaturated fats can reduce atherosclerosis risk by regulating several genes, particularly *APOA1*, *APOA5*, and *APOE* that are involved

**Table 1.** Influence of nutraceuticals and dietary components on cancer

<b>Nutraceuticals</b>	<b>Sources</b>	<b>Type of cancer</b>	<b>Beneficial or pathological effects</b>	<b>Ref.</b>
Indole-3-carbinol	Broccoli, Brussels sprouts, cabbage, collards, cauliflower, kale, mustard greens, turnips, and rutabagas	Lung cancer	Indole-3-carbinol induces apoptosis through p53 and activation of caspase-8 pathway in lung cancer A549 cells.	[59]
Isothiocyanates	Broccoli, watercress, Brussels sprouts, cabbage, Japanese radish, and cauliflower	Bladder cancer	Isothiocyanates may inhibit bladder carcinogenesis through epigenetic modulation of gene expression associated with histone H1 phosphorylation.	[60]
Sulforaphane	Broccoli sprouts, cruciferous vegetables such as cabbage and cauliflower	Ovarian cancer	Sulforaphane suppresses tumor growth by inhibiting ovarian cancer cell proliferation by targeting tumor-related signals.	[61]
Allicin	Allicin is a compound produced when garlic is crushed or chopped	Gastric cancer	Allicin inhibits proliferation and induces apoptosis in SGC-7901 cancer cells.	[62]
Catechin	Tea, chocolate, apples, pears.	Lung cancer	Catechin is an immune checkpoint inhibitor in lung cancer.	[63]
Caffeine	Beans of coffee, cacao, and guarana plants	Colorectal cancer	Caffeine inhibits proliferation, viability, invasiveness, and metastasis, as well as acts as effective adjuvant during chemotherapy of colorectal cancer.	[64]
Theophylline	Cocoa beans	Breast cancer	Theophylline reduces the necrotic effect of berberine as well as induces cell cycle arrest and PARP, HMGB1, Bcl-2 family mediated apoptosis in MDA-MB-231 breast cancer cells.	[65]
Daidzein and genistein	Tempeh, tofu, soybeans	Prostate cancer	Daidzein and genistein inhibit oxidative stress and inflammatory mediators.	[66]
Resveratrol	Peanuts, pistachios, grapes, red and white wine, blueberries, cranberries	Anaplastic thyroid cancer (ATC)	Resveratrol overcomes retinoic acid resistance in ATC cells by reprogramming CRABP2/RAR- and fatty acid-binding protein 5 (FABP5)/PPAR- $\beta/\delta$ -mediated RA signaling.	[67]
Pterostilbene	Berries (particularly, blueberries ) and nuts	Pancreatic cancer		[68]
Limonene	Citrus fruits, such as lemons, limes, and oranges	Prostate cancer	D-limonene enhances the antitumor effect of docetaxel against prostate cancer cells without affecting the normal prostate epithelial cells.	[70]
Selenium	Brazil nuts, seafood, and organ meats	Skin cancer	Selenium compounds act as adjuvant therapy for cancer.	[71]
Vitamins A, C, D and folic acid	Carrots, sweet potatoes, winter squash, green and red peppers, spinach, cabbage, turnip, broccoli, Brussels sprouts, and oily fish such as salmon, sardines, herring, and mackerel	Colon cancer	Supplementation can reduce the risk for neural tube defects.	[72]

**Table 1.** (Continued)

Nutraceuticals	Sources	Type of cancer	Beneficial or pathological effects	Ref.
Short-chain fatty acids (SCFA)	Barley, oatmeal, beans, nuts, and fruits such as apples	Colon cancer	SCFA intervenes with cholestyramine to prevent reabsorption of bile acids and also confers protection against hepatocellular carcinoma.	[73]
Probiotics	Yogurt, kefir, kombucha, sauerkraut, pickles, miso, tempeh	Colorectal cancer	Probiotics improve the host's immune response and counteract proliferation of cancer cells through regulation of apoptosis and cell differentiation.	[74]

in lipid metabolism<sup>[140,141]</sup>. Some SNPs alter a metabolic response to a nutrient rather than shifting the requirement for it. For example, the rs3135506 polymorphism in *APOA5* modifies the effect of high-fat diet on blood pressure<sup>[142]</sup>.

As an example of metabolic disorder, phenylketonuria, which is caused by a mutation in the *PAH* gene, can be managed by proper dietary management<sup>[143]</sup>. Several mutations were found in the genes of rate-limiting proteins, such as galactose-1-phosphate uridylyltransferase<sup>[144]</sup>, phenylalanine hydroxylase, and glucose-6-phosphate dehydrogenase<sup>[145]</sup>. The anthocyanin and polyphenol can modulate paraoxonase1 (*PON1*) activity, and it is recognized that the activity of *PON1* can be regulated at the genetic level as its SNPs exhibit a strong association with its activity. It has been reported that a diet rich in polyphenols and anthocyanins can modulate *PON1* activity and its expression<sup>[18]</sup>. Polyphenols and anthocyanins consumption may evoke protection against the deleterious effect of *PON1* gene polymorphism and reduce cardiovascular risk. *PON1* is associated with the circulatory levels of high-density lipoprotein (HDL) and is the primary determinant of antioxidant and anti-inflammatory activities of HDL, and at the molecular level, promotes HDL-mediated macrophage cholesterol efflux. The *PON1* variants could be used as biomarkers in stratifying individuals who might advantage from the targeted dietary recommendation and preventive medicine strategies<sup>[18]</sup>.

## 6. Role of nutritional genomics in personalized nutrition

It is clear from the above discussion that an effective way to get hold of the best possible health effects in general, and in cancer and MetS patients, is to optimize the diet specifically tailored to individuals, considering their metabolic requirements. Nutritional genomics approach is widely used to evaluate the alterations in genomic profile in response to dietary nutrients and to develop novel strategies that can be applied in personalized nutrition and medicine. Subsequently, it may help with the effective management of diet-related diseases by administering individualized nutritional consultation according to the individuals' genetic profiles. By analyzing the potential

response to a cluster of nutrients, it is probable to propose a diet tailored to an individual to inhibit processes associated with specific malignancies.

Studies have shown that specific genes and their variants can be regulated or influenced by nutrients or food compounds from the diet. By predicting the functional interactions between nutrients and genomes, the emerging and developing field of personalized medicine incorporates nutrition into its personalized therapy for cancer and MetS. This is based on the abilities of certain nutrients that can activate inhibitory mechanisms against cancer, including apoptosis and impairment to angiogenesis<sup>[8-10]</sup>. Furthermore, the impact of diet on MetS is mediated through a complex network of genes which can be effectively investigated through nutritional genetics or nutritional genomics means.

## 7. Conclusion

This review expounds the potential role of several types of natural compounds for treating cancer and MetS in line with the principles of nutritional genomics. To increase humans' lifespan, different aspects such as gene-nutrient interaction, alterations in diet, and nutritional treatment of genome instability should be considered and studied thoroughly. On the one hand, some dietary constituents can have beneficial effects on cancer prevention. On the other hand, they can enhance cancer progression through metastasis. To abrogate adverse consequences of nutraceuticals on tumors, each compound or group of compounds should be investigated at different phases of cancer development.

## Conflict of interest

The authors declare no conflict of interest.

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**Table 2.** Influence of nutraceuticals and dietary components on MetS

Nutraceuticals	Sources	Types of MetS	Beneficial or pathological effects	Ref.
Omega-3 fatty acids	Salmon, mackerel, tuna, herring, sardines, nuts, seeds (e.g., flaxseed, chia seeds, and walnuts), and plant oils (e.g., flaxseed oil, soybean oil, and canola oil)	Schizophrenia and MetS	Omega-3 fatty acids have beneficial effects on triglyceride metabolism in schizophrenia and MetS.	[96]
Omega-6 fatty acids	<ul style="list-style-type: none"> <li>Poultry, eggs, nuts,</li> <li>sesame seeds, cereals, wheat, whole-grain bread, and pumpkin seeds</li> </ul>	Insulin resistance syndrome and atherosclerosis	Omega-6 fatty acids may reduce insulin resistance syndrome, lipid and lipoprotein metabolism, and atherosclerosis.	[97]
Linoleic acid	<ul style="list-style-type: none"> <li>Vegetable, oils, nuts, seeds, meats, and eggs</li> </ul>	Coronary artery diseases and type 2 diabetes mellitus	Increased dietary intake or tissue levels of linoleic acid is associated with a reduced incidence of CVDs (mainly coronary artery diseases) and of new-onset metabolic syndrome or type 2 diabetes mellitus	[98]
Arginine	Nuts (e.g., walnuts, hazelnuts, pecans, peanuts, almonds, cashews, and Brazil nuts), seeds (e.g., sesame and sunflower seeds), oats, corn, cereals, buckwheat, brown rice, dairy products, meat, chicken, and chocolate	Stroke in pediatric mitochondrial disease	Arginine therapy yields significant therapeutic benefits with little risk in the stroke in pediatric mitochondrial disease.	[99]
Leucine	Fish, salmon, pink, raw, wheat germ, almonds, and chicken	Obesity, type 2 diabetes mellitus, and MetS	Leucine interacts with the insulin signaling pathway to stimulate downstream signal control of protein synthesis, resulting in muscle protein maintenance during periods of restricted energy intake. Leucine also appears to modulate insulin signaling and glucose use by skeletal muscle.	[100]
Hydroxyisoleucine	Meat, fish, poultry, eggs, cheese, lentils, nuts, and seeds.	Type 2 diabetes mellitus, obesity, and dyslipidemia	Hydroxyisoleucine stimulates glucose-dependent insulin secretion by a direct effect on pancreatic islets.	[101]
Lactotripeptides (valine-proline-proline)	Dairy food	Hypertension	Lactotripeptides (isoleucine-proline-proline/valine-proline-proline) improves blood pressure and arterial stiffness in subjects with suboptimal blood pressure control and MetS.	[102]
Isoflavones	Soy and its products, and legume seeds (lentils, beans, peas)	MetS	Isoflavones may contribute to insulin sensitization and improve lipid homeostasis.	[103]



**Table 2.** (Continued)

Nutraceuticals	Sources	Types of MetS	Beneficial or pathological effects	Ref.
Casein	Milk, yogurt, cheese, and other dairy products	MetS	Casein improves insulin sensitivity, lowers blood pressure, activates PKC beta II, and restores renal function.	[104]
Flavonoids	Vegetables, fruits, seeds, cereals, wine, tea, and certain spices	Obesity and atherosclerosis	Flavonoids reverse obesity and improve MetS and atherosclerosis	[105]
Chlorogenic acid	Apples, artichoke, betel, burdock, carrots, coffee beans, and eggplants	CVD, liver disease, and MetS	Chronic dietary intake of chlorogenic acid attenuates diet-induced inflammation as well as cardiovascular, liver, and metabolic changes.	[106]
Vitamins	Vitamin A (e.g., carrots, sweet potatoes, spinach, kale), Vitamin B12 (e.g., meat, poultry, fish), and Vitamin E (e.g., nuts, seeds, vegetable oils)	MetS	Lack of biologically active form of vitamins is a risk factor for metabolic syndrome.	[107]
Minerals	Meat, cereals, fish, milk, dairy products, fruit, vegetables, and nuts.	MetS	Some trace elements, but not all, are linked to the development of MetS.	[108]

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**Table 3.** Disorders and their corresponding genetic biomarkers

Disorders	Genetic biomarkers	Ref.
Liver cancer	<i>FGFR</i> , <i>VEGFR</i> , <i>PD-1</i> , <i>PDGFR</i>	[118]
Colorectal cancer	<i>MLH-1</i> , <i>MSH-2</i> , <i>MSH-6</i> , <i>PMS-2</i> , <i>EPCAM</i> , <i>APC</i> , <i>POLD1</i>	[119]
Squamous cell carcinoma	<i>ADAM15</i> , <i>CDC7</i> , <i>IL12RB2</i>	[120]
MetS	<i>APO-B/APO-A1</i>	[121]
Cancer in the liver and other sites	<i>CYP2E1</i>	[122]
Cancer in stomach, gastrointestinal tract, and nasopharynx	<i>GSTM1</i> , <i>CYP1A1</i>	[123]
MetS, particularly elevate insulin concentrations and insulin resistance	<i>ACC2</i> , <i>LEPR</i>	[6,124]
Monogenic obesity and MetS	<i>IL-1β</i> , <i>TCF7L2</i> , <i>LTA</i> , <i>IL-6</i> , <i>TNF-α</i> , <i>ACSL1</i> , <i>LEP</i> , <i>LEPR</i> , <i>POMC</i> , <i>MC4R</i>	[125]
Abdominal obesity	<i>STAT3</i>	[126]
Monogenic diabetes	<i>HNF-4α</i> , <i>GCK</i> , <i>HNF-1α</i> , <i>IPF-1</i> , <i>HNF-1β</i> , <i>NEUROD1</i>	[127]
Type 2 diabetes mellitus	<i>CAPN10</i> , <i>TCF7L2</i> , <i>FTO</i> gene on chromosome 16	[128]
Hypertriglyceridemia	<i>CAPN10</i>	[129]
Body mass index abnormalities	<i>CAPN10</i> , <i>BDNF</i> , <i>FTO</i> gene on chromosome 16	[130]
Hypertension and insulin resistance	<i>ACE</i> , <i>AGT</i> , <i>AGTRI</i> , <i>ADDI</i> , <i>NPPA</i> , <i>ADDRB2</i> , <i>SCNN1A</i> , <i>GNB3</i> , and <i>NOS3</i>	[131]
Obesity and diseases of the central nervous system	<i>LEPR</i> , <i>PRKCH</i> , <i>PACSI</i> and <i>RMST</i> , GPCRs	[132]
Obesity and early metabolic syndrome	<i>ADCY5</i> , <i>FADS1</i> , <i>GLIS3</i> , <i>IGF1</i> , polymorphisms in the genes of adiponectin ( <i>ADIPOQ</i> ) and its receptors ( <i>ADIPOR1</i> )	[133]

**Table 3.** (Continued)

Disorders	Genetic biomarkers	Ref.
Insulin receptor polymorphisms	<i>COBLL1/GRB14</i> , <i>IRS1</i> , <i>PDGFC</i> , <i>UHRF1BP1</i> , and <i>LYPLAL1</i>	[134]
Central adiposity	<i>APOA1/C3/A4/A5</i> cluster, <i>APOB</i> , <i>APOE</i> , <i>CETP</i> , <i>TCF7L2</i> , <i>GKPR</i> , <i>FABP</i> , <i>MTP</i> , <i>PPARγ</i> , <i>SCARB1</i> , and <i>PLIN</i>	[135]

FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; PD-1, programmed cell death protein 1; MLH1, MUTL homolog 1; MSH1, MutS homolog 1; MSH2, MutS homolog 2; MSH6, MutS homolog 6; PMS2, postmeiotic segregation increased 2; EPCAM, epithelial cell adhesion molecule; APC, adenomatous polyposis coli; POLD1, polymerase δ1; ADAM15, a disintegrin and metalloproteinase metalloproteinase domain 15; CDC7, cell division cycle 7 homolog; IL12RB2, interleukin 12 receptor beta 2; DCP1 or ACE, dipeptidyl carboxypeptidase 1; AGT, angiotensinogen; AGTR1, angiotensin II receptor type 1; ADD1, adducin 1; NPPA, natriuretic peptide precursor A; ADRB2, adrenergic receptor β-2; SCNN1A, sodium channel, nonvoltage-gated 1 alpha; GNB3, guanine nucleotide binding protein (G protein) beta polypeptide 3; NOS3, nitric oxide synthase 3; KSR2, kinase suppressor of Ras 2; GIPR, gastric inhibitory polypeptide receptor; GPCRs, G protein-coupled receptors; ACC2, acetyl-CoA carboxylase β; ADH, alcohol dehydrogenase; APO, apolipoprotein; ACSL, long-chain acyl coA synthetase; CTP, cytochrome p150; EPHX, epoxide hydrolase; GST, glutathione-S-transferase; IL, interleukin; LEPR, leptin receptor; LTA, lymphotoxin-α; PPAR, peroxisome proliferator-activated receptor; TCF7L2, transcription factor 7-like 2; TNF, tumor necrosis factor; POMC, pro-opiomelanocortin; MC4R, melanocortin 4 receptor; STAT3, signal transducer and activator of transcription 3; SRB1, scavenger receptor class B type 1; BDNF, brain-derived neurotrophic factor; HNF4α, hepatocyte nuclear factor 4 alpha; IPF-1, insulin promotor factor-1; CAPN10, calpain 10; ADCY5, adenylyl cyclase 5; APO, apolipoprotein; CETP, cholesterol ester transfer protein; FABP, fatty acid-binding proteins; GKPR, glucokinase regulatory protein; MTP, microsomal triglyceride transfer protein; PLIN, perilipin; SCARB, scavenger receptor class B type.

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