Nutritional Genomic: A Multi-Directional Approach to Address Complex Diseases with Multi-Functional Nutrition

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Abstract: Nutritional genomics describes the biological interactions between genes and diet, their effects on the metabolism, and susceptibility to develop diseases. This approach covers both nutrigenomics that explores the effects of nutrients on the genome; and nutrigenetics that explores the effects of genetic polymorphisms on diet/disease interactions. These interactions vary because individuals have unique combinations of common genetic polymorphisms that are differentially affected by diet. Diseases causality is associated to certain genetic polymorphisms providing predictive biomarkers for diagnostic accuracy. Specific nutrient can modify the expression of genes through the interaction with receptors that activate the transcription of target genes and affect signal pathways. Nutritional genomics is aimed to prevent onset of diseases and maintain human health, identify individuals who are responders and can benefit from specific dietary interventions, and identify how genetic variation affects human nutritional requirements. Nutritional genomics has many potential therapeutic and preventive applications: in individuals with a genetic predisposition to complex diseases including cancer, diabetes and cardiovascular disorders; in those already suffering from these diseases; and in those with memory impairment during aging. This review describes nutritional facts linked to genomic aspects to manage multigenic diseases. It presents some notable example of nutrients with proven modulating gene activity, and the role of nutrition associated with nutritional genomics. Hereafter we briefly review the health-promoting properties of two well-known edible plants, i.e. dandelion and artichoke whose presence in the diet could simultaneously exert positive influence on molecular genomic mechanisms related to risk factors for chronic diseases.

KEYWORDS: Food, gene-nutrient interaction, dandelion, artichoke, phytochemicals, minerals.

INTRODUCTION

Genes can be modulated by the environment and therefore influence on the risk of developing certain diseases. Specific genes expressions can be regulated through small changes in diet and either decrease or increase the incidence of various pathologies. In brief, a genetic predisposition to disease interacts with environmental factors; this interaction might be innocuous to people not carrying a specific combination of genes. As an example, some individuals with normal cholesterol levels are stricken by myocardial infarction at early age, while others appear to be immune to heart disease despite their sub-optima lifestyle, including smoking, poor diet, and non-controlled obesity. Yet, many diet-regulated genes are implicated in complex processes at genomic, proteomic, and metabolomic levels playing an important role in the onset, incidence, severity, and progression of certain diseases [1].

Nutritional genomic addresses these processes by a combination of nutrigenomic and nutrigenetic aspects. In brief, nutrigenomic helps understanding the etiologic aspects of chronic diseases such as cancer, diabetes, obesity, and cardiovascular disorders. Nutrigenetics, on the other hand, identifies how the genetic profile of a particular individual coordinates the different body responses to various dietary nutrients. It also reveals why and how people respond differently to the same nutrient. The ultimate goal of nutrigenetic is the study the individual genome susceptibility to what is currently called personalized or individualized nutrition [2-4]. Through nutritional genomic approaches, groups at high risk of complex diseases can be identified by learning the specific genetic variants associated with these pathologies and prevent or even delay the disease by taking specific nutrients [2-4]. Nutritional genomics has revealed that some genes regulated by active substances in the diet play a significant role in the onset, incidence, progression and severity of certain diseases.

Among the many examples of single-gene, aka monogenetic disorders that might be corrected with adequate nutrient intakes or drug therapy, phenylketonuria (PKU) results from a genetic variant (phenylalanine hydoxylase deficiency) that leads to deficient metabolism of the amino acid phenylalanine, which then becomes neurotoxic when accumulated during normal protein intake [5]. Individuals carrying a Gln27Glu mutation of the β-adrenoceptor 2 gene (ADRB2) or a Pro12Ala mutation of the PPARG2 gene and consuming a high carbohydrate diet are at greater risk of obesity [4]. Another example is that of common genetic variants among Japanese people that cause imbalances in regulatory protein toxins system and, consequently, increase the risk of developing stomach cancer. It has also thought that people following a diet

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that reduce total cholesterol levels experience marked effects, while others do not respond at all [3]. Obese patients also have increased lipogenic gene (SREBP1) expression, leading to elevated levels of triglycerides, fatty acid synthase, and malic enzyme. The final outcome is lipotoxicity, fatty liver, lipoapoptosis, endothelial dysfunction, and hyperglycemia. Studies have found that nutrients (Glycyrrhizic acid-the bioactive constituent of licorice roots, and resveratrol) which influence lipoprotein lipase (LPL) activity and lipogenesis in the liver and in the adipose tissue are beneficial for this kind of disorders [6, 7]. Also, folate intake modulates the expression of the methylenetetrahydrofolate reductase (MTHFR) gene, whose disruption leads to increased plasma homocysteine levels, i.e. a major risk factor for vascular diseases [1]. Finally, different researches have associated greater vitamins D intake with a lower risk of certain diseases development. Vitamin D interacts with our genes through the vitamin D receptor (VDR). This receptor binds to the human genome at more than 2000 specific locations associated with autoimmune diseases like type I diabetes, multiple sclerosis, rheumatoid arthritis and Crohn's disease, as well as certain cancers, including leukemia and colorectal cancer [8].

While certain nutrients affect monogenetic diseases, most human diseases are the consequence of complicated processes that involved multiple genes; thereby, the understanding of multigenic diseases requires the knowledge of genetic alterations, which, in turn, are influenced by the complexity of the gene/environment interrelations. Simultaneous regulation of different metabolic pathways in complex disorders by dietary interventions would provide valuable opportunities to control chronic diseases.

Genetic Biomarkers Common to Complex Multigenic Diseases

A genome wide association (GWA) approach has been exceptionally effective in identifying genetic variants associated with disease risk. It appears that specific alterations are crucial to processes associated with disease causality, providing predictive genetic targets currently used for diagnostic, prognostic, therapeutic considerations, and development of new strategies for effective novel treatments [9]. Many of these variants are shared by different diseases. Recent GWA studies of 2,000 cases have showed 3,000 shared biomarker genetic controls for seven complex human diseases of major public health importance – bipolar and coronary artery disorders, Crohn's disease, hypertension, rheumatoid arthritis, and diabetes [10]. Recognition that disease susceptibility arises through the combination of multiple genetic pathways where certain genetic alterations are shared suggests that some multigenic diseases could have a common molecular origin [11]. Examples of multigenic disorders are Alzheimer's and Parkinson's diseases and bipolar affective disorders, which share single nucleotide polymorphisms (SNPs) in the microtubule-associated protein tau (MAPT), in the gene encode for glycogen synthase kinase 3 beta (GSK3β), and in the FAT family genes [12].

Genetic research has also demonstrated complex interplays in autoimmune diseases. From rheumatoid arthritis to multiple sclerosis, lupus erythematosus, and inflammatory bowel disease (Crohn's disease and ulcerative colitis) some common genetic etiology is shared, which clarifies the basic pathophysiology of these entities and allows correct therapeutic approaches [13]. As an example, the NALP1 protein is one of the many receptors for bacterial or viral signals against infection identified in several autoimmune diseases and is currently used to search signals that trigger these diseases [13]. Type 1 diabetes and celiac disease are also caused by atypical underlying mechanisms, such as autoimmunity-related damage by intolerance to certain nutrients. Four type 1 diabetes loci seem to be associated with celiac disease (PTPN2, CTLA4, SH2B3, chromosome 3p21 variant) and three celiac disease loci are associated with type 1 diabetes (RGS1, IL18RAP, TAGAP) [14]. Diseases sharing genetic causes suggest they could also share environmental triggers factors. Diabetes mellitus is associated with several mitochondrial gene mutations (MtDNA). Maternally inherited diabetes and deafness (MIDD) is associated with the 3243 mutation, a typical mutation of MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) that affects particularly the brain, nervous system and muscles [15]. About 1% of patients with diabetes mellitus carry the 3243 mutation having also been found MtDNA mutations in patients with other diseases such as cardiomyopathy, migraine, cluster headache, and deafness [15].

In brief, the fact that several gene mutations are linked to different pathologies opens new potential

fields of investigation to treat or, better yet, prevent the development of many complex pathologic processes.

Examples of Nutritional Approaches to Multigenic Diseases

In this section, we will list some notable examples of nutrients with proven gene-modulating activities (Table **1**).

(a) Dietary Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) such as the precursors linoleic (18:2ω6) and linolenic (18:3ω3) acids cannot be synthesized by mammals and must be obtained from the diet or through supplements/functional foods. Long-chain ω3 PUFAs are mostly found in marine products, whereas the main sources of dietary ω6 PUFAs are vegetable oils and meats. Adequate intakes of PUFAs have been shown to lessen the risk of several human diseases, including obesity, diabetes, heart disease, and stroke [16]. From a mechanistic viewpoint, PUFAs also act at the nuclear level and affect the expression of genes involved in diverse metabolic pathways. In particular, PUFAs act via nuclear receptors such as peroxisome proliferator activated receptor α (PPARα) and liver X receptor a (LXRα), and through the transcription factor sterol regulatory element binding protein-1c (SREBP), to produce favorable hypolipidemic phenotypes [16]. ω3 PUFAs have also been shown to promote fatty acid oxidation while decreasing the rates of lipid synthesis [17], resulting in decreased plasma lipid concentrations and enhance insulin sensitivity [17]. Several significant gene–PUFA interactions have been found, indicating regulatory effects of PUFA by gene variants of IL-2, IL-6, IL-18, TNF receptor family member 1B and 21, leptin receptor and adiponectin on obesity risk. After stratification by genotype, the strongest effects were found for rs2069779 (IL-2) and all tested PUFA as well as for rs1800795 (IL-6) and linoleic or arachidonic acid [18].

Table 1. Examples of Nutrients (Phytochemicals, Minerals and Polyunsaturated Fatty Acids) with Proven Gene-Modulating Activities

Nutrients		Compounds	Health benefits
Phytochemicals	Polyphenols	Resveratrol	Antiangiogenic, anti-inflammatory, and antiviral activities
		Curcumin	Anticancer, antiviral, antiarthritic, antiamyloidal, antioxidant, and anti-inflammatory activities
		Quercetin	Anti-inflammatory, antioxidant and antitumor activities
		Luteolin	Anti-proliferative activity, promoter of carbohydrate metabolism, neuroprotective activity and immune system modulation
		Ferulic acid	Antitumor activity
		Epigallocatechin gallate	Interfere with various processes leading to cancer, atherosclerosis, and neurodegenerative diseases
		Proanthocyanidins	Neuroinflammation control
		Isoflavones	Protection against some hormone-driven forms of cancer and preventive role toward cardiovascular disease
	Terpenes	Carotenoids	Preventing the development of inflammation-associated diseases such as atherosclerosis, rheumatoid arthritis, and cancer
		Tocopherols	
	Sterols	Sitosterol, Stigmasterol Campesterol	Reduce intestinal cholesterol absorption
	Sulfur components	Allyl sulfur compounds	Inhibition of carcinogenesis
Minerals		Calcium, Potassium Magnesium	Regulation of blood pressure and of serum lipids
		Selenium	Involves in thyroid hormone metabolism, antioxidant defense, redox systems, and maintenance of normal liver function
		Zinc	Involved in metabolism of proteins, lipids, and carbohydrates
		Cupper	Involved in antioxidant defense
Polyunsaturated fatty acids		ω3 PUFAs ω6 PUFAs	Promote fatty acid oxidation while decreasing the rates of lipid synthesis

(b) Minerals

Minerals such as calcium, potassium and magnesium have multiple actions on human physiology, such as regulation of blood pressure and of serum lipids [19, 20]. Relevant to the latter, calcium and magnesium form intestinal insoluble soaps with fatty acids, resulting in a decrease in dietary fat absorption, in turn leading to a reduction in serum cholesterol level, decreased production of VLDL and increased uptake of LDL by the liver [19]. Selenium also exerts important health effects, particularly in relation to cancer and to the immune response, specifically modulating lymphocyte and neutrophil functions. Clinical studies report that increasing selenium intake decreases infection and susceptibility to viral mutations [21]. Selenium affects cell function through selenoproteins, which have important enzymatic functions in relation to thyroid hormone metabolism, antioxidant defense, redox systems, and maintenance of normal liver function [21]. In addition, zinc, iron, and copper are essential metals for different physiological functions. Zinc plays a crucial role in cell membrane integrity and is the component of more than 300 different enzymes involved in metabolism of proteins, lipids, and carbohydrates. Iron is essential for cellular proliferation and for maintaining cell viability. Cupper functions as the active centre of cuproenzymes such as cytochrome c oxidase, which is a component of the mitochondrial respiratory chain, and Cu,Zn-superoxide dismutase, which is involved in antioxidant defense [20, 22]. To illustrate the gene-diet interactions related to mineral metabolism, we mention several examples reviewed in Fleet *et al*. [20]. First, there are data available that suggest the response to changes in dietary iron is dependent upon genetic factors. Although C282Y mutation in the HFE gene is present in 85% of adult cases of the iron overload disease hemochromatosis, only one-third of the individuals with the HFE mutation experience the clinical consequences of the disease. Another example of a potential gene-diet interaction affecting minerals metabolism is for calcium. There are racial differences in how young girls adapt to dietary calcium restriction. When girls were provided controlled diets containing high, medium, or low levels of calcium, adaptation to low dietary Ca intake was strong in black girls and only modestly affected by diet in the white girls [20].

(c) Phytochemicals Modulating Gene Expression

Plant-based foods contain high amounts of phytochemicals that can modulate several enzymatic and chemical reactions in the human body [23]. A large number of epidemiological studies correlate high consumption of phytochemicals with lower risk of cardiovascular disease and diabetes [24, 25]. Several mechanisms by which phytochemicals may be protective against cardiovascular diseases have been proposed, including antioxidant, anti-platelet, and anti-inflammatory effects and improved endothelial function. Notably, the vast majority of these effects have been reported *in vitro*.

The largest group of phytochemicals that are being investigated for their health benefits is that of polyphenols. Epidemiological studies strongly suggest that polyphenols exert protective action on a large number of pathological conditions, including cardiovascular and metabolic disorders, infections, cancer, autoimmune diseases, and neurodegenerative processes (e.g. rheumatoid arthritis, Parkinson's and Alzheimer's diseases, multiple sclerosis) [24, 26].

One fashionable example is that of resveratrol, the phytoalexin found (in minute amounts) in polygunum cuspidatum and berries. *In vitro* studies suggested antiangiogenic, anti-inflammatory, and antiviral properties [27], translating into higher longevity (shown in lower organisms) [28].

Curcumin - from the spice turmeric- has also been suggested to possess a wide range of health benefits such as anticancer, antiviral, antiarthritic, antiamyloidal, antioxidant, and Anti-inflammatory properties [29]. Also curcumin regulates numerous molecular targets, included transcription (NF-kB, STAT3, PPARγ) and growth (VEGF) factors, inflammatory cytokines (TNF, IL-1, IL-6), protein kinases (mTOR, MAPK, Akt), other enzymes (COX2, 5-LOX), and important signaling pathways [29]. This phytochemical improves obesity-associated inflammation and metabolic disorders such as insulin resistance, hyperglycemia, hyperlipidemia, and hypercholesterolemia [30]. It has also been suggested that in severe asthma and in chronic obstructive pulmonary disease patients and appears to be important in controlling differentiation adipocytes and growth of cancer cells [29].

Quercetin is found in apples, tomatoes, onion, lettuce, citrus fruit, broccoli, cherries, wine, and tea. It possesses Anti-inflammatory, antioxidant and antitumor properties [31] and inhibits the production of pro-inflammatory enzymes such as interleukin-6 (IL-6) in lipopolysaccharide-stimulated neutrophils [28].

Luteolin is a flavonoid found in carrots, peppers, and cabbage with strong anti-proliferative activity against different human cancer cell lines. It effectively inhibits proliferation of human leukemia cells, and plays an important role as promoter of carbohydrate metabolism [32]. Moreover luteolin inhibits platelet activating factor and suppresses the inflammatory response induced by allergens; recent studies have shown that luteolin possess neuroprotective properties distinct from its well-known anti-oxidant effects. In particular, luteolin is an immune system modulator that reduces brain inflammation and has important implication in various neurodegenerative disorders, including Alzheimer's disease [33].

The hydroxycinnamic acid and ferulic acid are found in cereal grains such as rice, wheat and oats, and in coffee beans, apples, artichoke, peanuts, oranges and pineapples. Ferulic acid is reported to have pro-apoptopic effects in cancer cells, along with antitumor activity against breast cancer [34]. It is also a powerful antioxidant, and may scavenge oxygen free radicals, provide protection of DNA against oxidative damage [35].

Epigallocatechin gallate is a major component of green and other teas and also of cocoa beans. It has been suggested to interfere with various processes leading to cancer, atherosclerosis, and neurodegenerative diseases and is involved in the suppression of vascular endothelial growth factor and angiogenesis [36].

Proanthocyanidins are the most common type of tannins found in berries, cereals, and beans. Importantly, they control neuroinflammation by inhibiting the expression of inflammatory genes, and modulate the intracellular antioxidants level that protects from ischemia and cardiovascular disorders [37, 38].

Isoflavones are phytostrogens that have been the subject of considerable scientific research in recent years. Beside their purported health benefits related to protection against some hormone-driven forms of cancer such as prostate and breast cancer, there is an interest in their possible preventive role toward cardiovascular disease - namely as brought about by lower cholesterol levels - and osteoporosis following improved bone density. They may also beneficial against obesity and diabetes, inflammation processes, arthritis, and neurodegenerative diseases [39].

A wide range of others phytochemicals include terpenes (or isoprenoids) lipid-soluble compounds that exhibit a wide array of biological actions. Terpenes modulate neurotransmitter receptors, transporters, or ion channels, thus affecting neuronal, cardiac, or muscular functions. Studies reveal that carotenoids and tocopherols are immunomodulators and anti-inflammatory agents, preventing the development of inflammation-associated diseases such as atherosclerosis, rheumatoid arthritis [40], and cancer [41]. In addition, β-carotene inhibits inflammatory gene expression in lipopolysaccharide-stimulated macrophages, and the antioxidant activity of β-carotene has been suggested to contribute to these beneficial effects [42].

Dietary plant sterols or stanols with sitosterol, stigmasterol and campesterol being most common reduce intestinal cholesterol absorption, thus lower plasma LDL cholesterol concentration in humans [43]. Their role in the modification of gene expression involved in cholesterol transport and metabolism is associated to several intestinal genes and transcription factors are candidates for regulation by plant sterols but they also play a role in regulating the expression of cholesterol homeostasis genes in the liver [43].

Garlic has reputation as a protective agent against cardiovascular disease. The health benefits of garlic, including inhibition of carcinogenesis, are supported by several epidemiologic and laboratory findings [44]. As an example, garlic sulfur components have been reported to suppress experimentally-induced tumor incidence in several organs, including the colon. Studies in humans also suggest that dietary garlic constituents reduce the risk of colorectal polyps that are considered precursors to colon cancer [45].

The mechanisms by which dietary phytochemicals of nutritional interest play a role in cellular response and in preventing pathologies have been widely reviewed [23-25]. Their direct interaction with nuclear receptors and their ability to modulate the activity of key enzymes involved in cell signaling and antioxidant responses make them responsible for their modulators role [46].

Edible Plants with Multiple Healthful Properties: their Potential to Modulate Multigenic Diseases

Most edible plants produce a wide array of phytochemicals, which are currently in clinical trials to

Table 2. Potential Preventive and Curative Roles in Metabolic Disorders of Dandelion and Artichoke

Dandelion *(Taraxacum officinale)*	Pharmacological uses	Artichoke *(Cynara scolymus)*
in vitro and animal studies	Antioxidants	*in vitro* and animal studies
in vitro and animal studies, clinical trials	Inflammations	*in vitro* and animal studies
in vitro and animal studies	Hypolipidemias	animal studies, clinical trials
in vitro and animal studies	Diabetes mellitus	animal studies, clinical trials
in vitro studies	Thrombi and ischemia	
in vitro and animal studies	Cancer	*in vitro* and animal studies
in vitro and animal studies	Liver complaints	*in vitro* and animal studies, clinical trials
in vitro and animal studies, clinical trials	Gastroenterology	*in vitro* and animal studies, clinical trials

be tested in a variety of diseases. We hereafter briefly review two well-known edible plants, i.e. dandelion and artichoke and outline their potential preventive and curative roles in metabolic disorders (Table **2**).

Dandelion (*Taraxacum officinale*)

The therapeutic properties of dandelion have been in part ascribed to its bitter principles e.g., sesquiterpenes typical of members of the *Asteraceae*. In addition, it contains taraxacoside and taraxinic acid β-D-glucopyranoside, 11,13-dihydrotaraxinic-acid β-D-glucopyranoside as well as ρ-hydroxyphenylacetic acid [47]. Others constituents from dandelion include various triterpenes and phytosterols such as taraxasterol, ψ-taraxasterol, their acetates and their 16-hydroxy derivatives arnidol and faradiol, α- and β-amyrin, β-sitosterol, β-sitosterol-β-D-glucopyranoside and stigmasterol [47]. Importantly, dandelion contains a plenty of phenolic compounds being the most predominant hydroxycinnamic and dicaffeoyltartaric acids and their derivates particularly caffeic acid esters and several caffeoylquinic acid isomers such as monocaffeoyltartaric, 4-caffeoylquinic, chlorogenic, caffeic, ρ-coumaric, ferulic, ρ-hydroxybenzoic, protocatechuic, vanillic, syringic and ρ-hydroxyphenylacetic acids as well as coumarins (umbelliferone, esculetin, scopoletin, cichoriin and aesculin), and various flavonoid glycosides such as luteolin, isorhamnetin, apigenin and quercetin derivates, among others [47, 48]. Besides phenolic compounds and bitter substances, dandelion contains high amounts of inulin, the storage carbohydrate characteristic of *Asteraceae*, and the amino acids glutamine and asparagines. Furthermore, dandelion is a rich source of vitamins (A, C, D, E, and several B vitamins) and minerals (iron, silicon, magnesium, zinc and manganese) in addition to having high potassium content.

In the recent past, particular attention has been given to the putative heath-promoting properties of dandelion's constituents, including choleretic, diuretic, anti-inflammatory, anti-oxidative, anti-carcinogenic, analgesic, hypoglycemic, anti-coagulatory and prebiotic effects [49].

Respect to diabetes and its complications several studies done with diabetic animals point to the beneficial properties of dandelion. In particular, it appears that certain dandelion extracts exert both insulin secretagogue and hypoglycemic activities [50, 51]. Different research groups have also indicated that dandelion regulates other metabolic disorders. In fact, studies report the influence of both water and alcohol extracts on hypertriglyceridemia, hypercholesterolemia, and hypertension, i.e. all independent risk factors of cardiovascular disease [48]. Moreover, *in vivo* studies targeting oxidative stress, inflammation and lipid profiles show that dandelion produces a significant fall in plasma and hepatic triglyceride and total cholesterol concentrations [52]. All of these activities can be related to preventive and ameliorative activities toward the metabolic syndrome and also affect processes such as coagulation alteration and higher blood viscosity. In brief, dandelion may reduce the risk of developing atherosclerosis via anti-oxidative, anti-inflammatory, and hypolipidemic activities [52] brought about by some of its low-molecular polysaccharide, triterpene, and steroid components. Finally, dandelion has been shown to be a powerful angiogenesis

inhibitor and reduces blood vessels that accumulate in fat tissues [53].

Mechanistically, inflammatory processes are connected with several disorders: many research studies have proven the anti-inflammatory properties of dandelion [52]. This protective role of dandelion is ascribed to its polyphenolic constituents that regulate pro-inflammatory mediator (IL-6, TNF-α) levels, NO and prostaglandin production in macrophages [54]. Dandelion's anti-inflammatory activities have also been observed in cell astrocytes [55].

It is noteworthy that dandelion possesses a marked antioxidant activity, shown in both biological and chemical models. In particular, the efficacy in inhibiting both reactive oxygen species (ROS) and nitric oxide (NO) generation have been attributed to its high phenolic content, in particular flavonoids such as luteolin derivates and coumaric acid derivatives [47,48].

Concerning chemoprevention, some anti-carcinogenic effects of dandelion have been proven *in vivo* and implicate cell proliferation and the inhibition of metastases formation due to increased apoptosis, as shown in human cells [56]. Others studies have demonstrated the potential of dandelion to block the growth of breast and prostate human cancer cells, suggesting that this herb might be a valuable and novel anti-cancer agent [57].

Finally, we should mention that inulin from dandelion acts as a prebiotic and might favor the enhancement of the immune function, notably in children [58,59].

The mechanisms of action through which dandelion's phytochemicals exert their activities are manifold; many have been identified and involve multiple cell-signaling pathways and molecules such as NFκB, Akt, MEK, ERK, sVCAM-1, MAPK, MMPs, TNF, IL, among others (reviewed in [49]).

Artichoke (*Cynara scolymus*)

Artichoke is another member of the *Asteraceae* family, widely cultivated in Mediterranean and American countries. Artichoke´s heads are an important component of the Mediterranean diet and a rich source of phenolic compound, inulin, fibers and minerals [60]. In addition to being consumed as foods, artichoke's heads are also employed in various galenic preparations. Indeed, artichokes are ancient medicinal plants; their therapeutic potential was known to the ancient Egyptians, Greeks, and Romans [60]. Its leaves are still used in European traditional medicine for the treatment of hepatitis, hyperlipidemia, obesity, and dyspeptic disorders [61,62], mostly due to the choleretic activities of *Cynara scolymus* [63].

In terms of active principles, artichoke is a rich source of polyphenols, with mono-and dicaffeoylquinic acids as the major components. This plant also accumulates various caffeic acid (3,4-dihydroxycinnamic acid) depsides, positional isomers of caffeic acid esters of quinic acid [60]. Other phenolics compounds include the flavones apigenun and luteolin and the anthocyanidins cyanidin, peonidin, and delphinidin [64,65]. In addition, artichoke, like dandelion and others members of *Asteraceae* family, synthesizes and accumulates inulin as a reservoir of carbohydrates [60].

Clinical and pre-clinical trials are confirming the therapeutic potential of *Cynara scolymus* [62]. As an example, artichoke leaf extracts exhibit hepatoprotective, anti-oxidative, antibacterial, anti-HIV, bile-expelling, and diuretic activities as well as the ability to inhibit cholesterol biosynthesis and LDL oxidation [60].

The antioxidant activity of different extracts of artichoke has been determinate by different methods [66] reveling that extracts with the highest content in phenolic compounds exerted major antioxidant capacity and effect on bile flow and liver protection. Moreover, artichoke extracts have been proposed as endothelium-protecting agents due to their potent, concentration-dependent antioxidant properties measured in stimulated human umbilical endothelial cells (HUVECs) [67]. In addition, cultured rat and human hepatocytes were used to evaluate the hepatoprotective properties of polyphenolic extracts from the edible part of *Cynara scolymus*, showing that artichoke protected cells from the oxidative stress caused by glucose oxidase and had an apoptotic activity on a human liver cancer cell line [68]. Also, the influence of aqueous and ethanolic extracts from artichoke on intracellular oxidative stress stimulated by inflammatory mediators (TNF-α, LPS) and ox-LDL in endothelial cells and monocytes has been studied, showing that artichoke extracts have marked protective properties against oxidative stress [69]. The protective activity of the edible portion has also been confirmed in rat models [63,66].

Cynara scolymus facilitates the control of body weight and positively influences glucose and lipid metabolism in both animal and human models. A methanolic leaf extract was found to suppress serum triglyceride elevation in olive oil-loaded mice [61]. Studies have demonstrated that artichoke extracts administered intravenously to rats suppressed the accumulation of palmitic-1-^{14}C acid in serum lipids and epididymal fat pad tissue [70]. Furthermore, treatment with *Cynara scolymus* flowering head extracts (500-1500 mg/kg by gavage) resulted in a significant decrease of post-prandial glycemia in normal and genetically obese rats [71]. On the other hand, artichoke leaf extracts increase the activity of the human endothelial nitric-oxide synthase (eNOS) promoter, and eNOS mRNA and eNOS protein expression in HUVECs, suggesting protection against cardiovascular diseases [72]. Artichoke leaf extracts (1280 mg, 12 weeks) decreased plasma total cholesterol in humans with respect to control groups [73]. In another study, the efficacy of a dietary supplementation with an extract containing artichoke on glucose and lipid pattern was evaluated in 39 overweight subjects, treated for 2 months. The treatment (200 mg of flower extract/day) successfully controlled overweight and impaired glycemia [74].

As mentioned, artichoke contains inulin. The prebiotic effects of artichoke inulin have been demonstrated on *Bifidobacterium bifidum* cultures and also in mixed cultures of colonic bacteria. In addition, intervention studies in humans on prebiotic efficacy of inulin from artichoke (10 g/d) have shown significant increases of both bifidobacteria and lactobacilli levels, with little adverse gastrointestinal effects [75]. In a way, these data confirm the folk use of artichoke for gastrointestinal disturbances and spasms [62].

In summary, the succinct review of the health effects of dandelion and artichoke suggest their exploitation as functional plant foods or as supplements to be employed in the adjunct treatment of several complex metabolic diseases.

CONCLUSIONS AND FUTURE DIRECTIONS

Common genetic alterations appear to be involved in crucial processes linked with causality to different diseases. This explains why the same disease does not manifest itself in the same fashion in everyone and why many disorders are the result of mutually-dependent permissive factors. The probability to detect shared disease-associated gene allows establishing onset genetic patterns offering great possibilities to manage several risk conditions through the control of a single one. Nutritional genomics has many potential therapeutic and preventive applications. Notably, genetic diagnostic biomarkers for prevention, earlier diagnostic, prognostic and therapeutic considerations of disease pathogenesis are available at affordable costs.

Genomics approaches, including metabolomic, pharmacogenomic, and related strategies have finally elucidated how phytochemicals integrated in the diet might balance complex mechanisms, benefit human health, and permit a better understanding of the molecular interactions between genes and phytochemicals.

The examples of the edible plants dandelion and artichoke might translate into alleviation or treatments of some diseases, as well as their prevention through adequate diets. Finally, the perspective exists to develop multifunctional ingredients in a nutritional genomics context, maybe starting from these and other edible plants.

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