Review Article

Nutrigenomics: A way forward to Disease and Genetic disorder: A synthetic review

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Abstract

Millions of people around the world are malnourished or have illnesses connected to dietary inadequacies. Unbalanced nutrient consumption is directly linked to several diseases, including diabetes, cancer, and cardiovascular disease, which cause significant numbers of deaths on a national and international scale. According to information from nutritional biology, diet is an external element that can affect several morphological and physiological behaviors through altering gene expression patterns. By affecting several molecular systems in the human body, nutrients can change the physiological state. Investigating how nutrition affects the functional dynamics of genomes in this setting requires the science of nutritional genomics.

The fields of nutrigenomics and nutrigenetics are closely related; the former is used to study the impact of nutrients on gene expression in the human body, while the latter is employed to investigate the various responses of gene variants to dietary elements, nutrients, and the development of nutraceuticals. Moreover, nutrigenomics helps to explain how dietary changes in signaling pathways linked to many illnesses and disorders, such as cancer, diabetes, and other metabolic syndromes, occur. Maintaining good health requires proper nutrition, as deficiencies in vitamin D can lead to conditions like rickets and osteomalacia. Fortunately, advancements in genome or genetic engineering can aid in improving crops and providing essential nutrients for optimal bone health and overall well-being.

Keywords: Nutrigenetics, nutrigenomics, Diet and disease, epigenetics, personalized nutrition

1. Introduction

Human's physiological and genetic makeup plays a significant role in how they respond to various dietary components and nutrients.[1] This concept is integral to personalized nutrition. The study of nutrigenetics has made remarkable strides in comprehending how genetic variations affect levels of macronutrients and micronutrients, as well as an individual's reaction to dietary intake. These genetic variations are essential in supporting the creation of personalized nutrition plans, making it easier to go from traditional dietary recommendations to genome-influenced nutrition.[2] Despite this progress, there are obstacles that may hinder the widespread adoption of tailored nutrition, which is still an emerging field.[3]

Noncommunicable diseases (NCDs) are primarily associated with chronic exposure to specific food components and are prevalent among individuals who follow a junk food eating lifestyle in urban areas. Biomarkers play a crucial role in identifying nutritional disorders such as disruptions in cholesterol and triglyceride levels, hypertension, or fluctuations in blood sugar, serving as indicators of NCDs.[4]

They can be either single protein, metabolites, or specific physiological functions that can detect proteomic and metabolic changes in an individual's body, potentially contributing to a range of chronic diseases influenced by their specific genotype.[5]

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Human disorders are linked to almost 1000 genes, out of which 97 percent lead to monogenic diseases.[6] The most common example is lactose intolerance, which is a consequence of mutation in the lactase gene causes insufficient lactase production in the small intestine.[7] The population reported to develop lactose intolerance lack the ability to digest lactose present in dairy products and need to cut or exclude food containing lactose from daily diet and convert to products that are lactose-free to get rid gastrointestinal distress.[8]

Various molecular methods can be employed to diagnose DNA damage in individuals such as single base mutations, DNA strand breaks, telomere shortening, chromosome breakage or loss, and mitochondrial DNA damage.[9] Among these methods, most well-validated biomarker for studying DNA damage in nutritional genomic research include assessment of micronuclei in cytokinesis-blocked lymphocytes coupled with transcriptomics are employed for the analysis of mRNA copies from genes actively undergoing transcription.[10] This technique allows simultaneous analysis of gene expression levels for thousands of samples in a single assay. Recent research has revealed the unique gene expression patterns found in peripheral blood cells that are linked to various diseased states. Notably, these patterns have been observed in both breast tumors and leukemia cases.[11]These distinctive patterns are now being harnessed as valuable biomarkers for early disease detection purposes.

Nutrients exhibit transcription factors interacting with a receptor, which triggers gene expression. For instance, lac operon within a cell (e.g., bacterial cell), it remains in an inactive state if lactose is absent.[12] The lacI inhibitor gene attaches to the promoter region, preventing RNA polymerase from initiating transcription, thereby blocking DNA transcription. Conversely, when lactose is present, it interacts with the system and induces a structural conformational change in lacI, thereby disabling its ability to bind to the promoter.[13] Consequently, RNA polymerase can bind to the promoter region and initiate transcription of the structural genes (lacY, lacA, lacZ), ultimately leading to the production of proteins such as β-galactosidase, permease, and transacetylase. These proteins facilitate the uptake and enzymatic breakdown of lactose to generate energy.[7] This review aims to synthesize the current knowledge and evidence on the role of nutrigenomics in understanding and managing various diseases and genetic disorders. To conduct a narrative synthesis on the major studies, a search was performed in google scholar search engine. Using keywords allowed for the identification and review of key publications addressing the subject matter.

Objectives

- To Synthesize recent advancements in nutrigenomics research, including studies elucidating gene-diet interactions and their impact on health outcomes.
- To Identify key findings and trends in nutrigenomic approaches to disease management and prevention.

1. Cancer pathogenesis and Overview of cancer epigenetics

The significance of nutrigenomics in cancer treatment is now apparent. For cancer therapy interactions between nutrients and genes associated with cancer can enhance metabolic interventions. Moreover, the concept of personalized medicine that integrates nutrition and healthcare can be envisioned by assessing the relationship between patients' genomic profiles and their nutrient consumption. Yet, further translational research is required to incorporate nutrigenomics into cancer therapy. When a normal cell of an organism is induced by a carcinogen, it causes damage to the normal cell by activating cellular processes cellular, such as cell proliferation, immortalization, apoptosis evasion, angiogenesis, invasion, and metastasis. These activities are arbitrated by regulation of genes expression that play role in carcinogenesis and tumor suppression, DNA repair mechanism, detoxification of oxidative stress, and transcription factors.[14] Epigenetics is an emerging field with great potential for preventing and managing certain types of cancers and diseases. It

involves various molecular processes and epigenetic processes, such as methylation of DNA, non-coding regions of RNAs, telomerase activity and, modifications of histones, play a crucial role in controlling cancer cells. They do so by regulating enzymes like DNA methyltransferase and histone deacetylase, as well as non-coding RNAs, which have a significant impact on cancer cell behavior.[1] Epigenetic changes play a crucial role in the evolution and advancement of various types of cancer. For example, in cancer therapy, irregular methylation and modifications of DNA and histones have been observed, leading to the dysregulation of critical tumor suppressor genes and oncogenes. Similarly, abnormalities of microRNAs, has been linked to cancer progression and metastasis.[15] According to resent studies, incorporating phytochemicals, following specific dietary patterns, like the Mediterranean diet, can effectively hinder the development of cancer by influencing genetic expression through processes such as nutrigenomics and nutria-epigenomics. These findings further highlight the importance of a healthy and balanced diet in preventing carcinogenesis.[16]

1.1 Bioactive molecules and cancer

Phytochemicals are naturally occurring bioactive compounds found in plants that possess antioxidant, anti-inflammatory, and anti-angiogenic properties, which can be beneficial in the treatment of cancer .[17] The epigenetic diet is centered on incorporating specific phytochemicals such as combination of epigallocatechin-3-gallate, morin, caffeic acid phenyl ester, apigenin, genistein, curcumin, resveratrol, and sulforaphane. These powerful compounds have been shown to directly impact cancer cells by inhibiting their growth and spread and promoting cell death. Furthermore, they can suppress the activity of oncogenes, which drive the development of cancer, while also bolstering the function of tumor suppressor genes.[12]

Bioactive molecules are regulated by various genes which are involved in the metabolism of dietary compounds. Bioactive food ingredients have been investigated for their therapeutic role in pathogenesis of malignant cells. While some of these ingredients have been shown to have protective effects, others may increase the risk of cancer development, especially in genetically susceptible individuals. Bioactive food ingredients are typically found in fruits, vegetables, whole grains, and other plant-based foods. These ingredients include various vitamins, minerals, phytochemicals, and other compounds that have been shown to have biological effects in the body. For example, carotenoids, flavonoids, and other phytochemicals have been shown to have antioxidant and anti-inflammatory effects, which may help to protect against cancer development. On the other hand, some bioactive food ingredients have been shown to have pro-carcinogenic effects. For example, certain compounds found in grilled or charred meats are carcinogenic, and excess consumption of alcohol has been linked to an increased risk of several types of cancer.

The effect of bioactive food ingredients on cancer risk is likely to be influenced by a variety of factors, including an individual's genetic makeup, lifestyle factors (such as smoking and physical activity), and overall dietary patterns. For example, genetic variations in genes involved in xenobiotic metabolism may influence an individual's susceptibility to the carcinogenic effects of certain bioactive food ingredients. According to recent research, more than 500 bioactive food components have been identified as potential contributors to the development of cancer.[16]

1.2 Carcinogen metabolism gene

Phase I enzymes, which include cytochrome P450 enzymes, play a critical role in the initial oxidation, reduction, and hydrolysis of bioactive molecules in the body. These reactions can help to neutralize potentially toxic compounds and make them more water-soluble, allowing them to be eliminated from the body more easily.

However, some bioactive molecules may be transformed into even more toxic metabolites during

Phase I reactions, and this is where Phase II enzymes come in. Phase II enzymes, which include glutathione S-transferases, sulfotransferases, and glucuronidation enzymes, can further modify bioactive molecules by conjugating them with other molecules such as glutathione or sulfate, making them even more water-soluble and easier to eliminate from the body. The expression and activity of Phase I and Phase II enzymes are regulated by a variety of factors, including genetic variation, environmental exposures, and dietary factors. For example, certain compounds found in cruciferous vegetables, such as sulforaphane, have been shown to induce the expression of Phase II enzymes, while other compounds found in processed or charred meats may induce the expression of Phase I enzymes and increase the hazards of cancer development.[10]

1. Genetic factors, dietary choices, and coronary diseases

An individual's genetic makeup and their dietary choices play substantial roles in the development of cardiovascular diseases (CVD). Exploring the interactions between genes and diet has the potential to enhance prevention strategies and improve prognoses for CVD.

Due to significant heterogeneity in dietary and genetic exposures, a meta-analysis reported that among the evaluated variants, CETP (Cholesteryl ester transfer protein) and alcohol dehydrogenase (ADH1C) were the most frequently studied, showing interactions with alcohol that modified the risk of myocardial infarction (MI) and coronary heart disease (CHD). However, studies exploring other potential biological interactions, such as FADS gene and fatty acids, vitamin B6, vitamin B12, and folic acid, did not yield consistent findings.[6] Although several studies have investigated gene-diet interactions in relation to cardiovascular disease (CVD) risk, the existing literature is limited and lacks consistency in demonstrating clinically and public health impactful interactions. This inconsistency is mainly attributed to positive findings derived from non-replicated case-control studies.[18]

2. Nutrigenomics Application as treatment

Nutrigenomics can help identify specific genes or gene pathways that are involved in disease development and progression. This knowledge can be used to develop new drugs that target these genes or pathways, or to repurpose existing drugs that target similar pathways. Nutrigenomics can help identify genetic variations that affect an individual's response to drugs, which can help in the development of personalized medicine. For example, genetic testing can identify patients who are likely to experience adverse side effects from a particular drug, allowing clinicians to adjust dosages or select alternative treatments. This approach has the potential to improve patient outcomes while reducing the burden of treatment-related adverse effects.

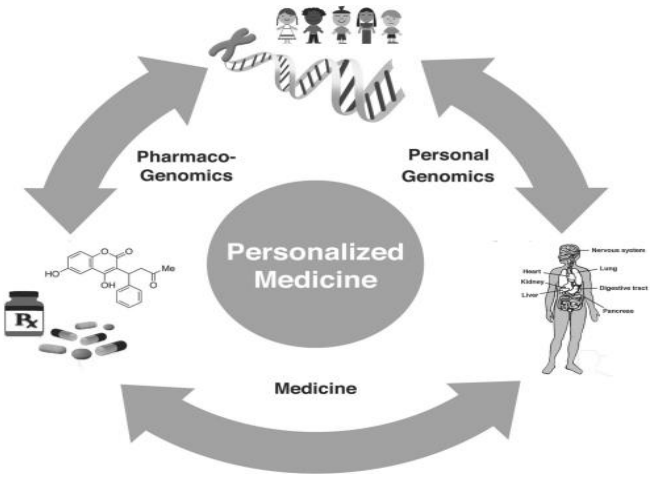

Figure 1: Interlinked relation of genomics and drugs

Nutrigenomics can help identify specific biomarkers or tag proteins to track the disease progression, treatment efficacy, and toxicity of trials. These biomarkers can be used to develop more effective therapies, and to identify patients who are most likely to benefit from a particular treatment. Nutrigenomics can help optimize clinical trials by identifying patient populations that are most likely to respond to a particular drug, and by identifying genetic variations that may affect drug efficacy or

toxicity. This knowledge can help streamline clinical trials, reduce costs, and improve patient outcomes.

Nutrigenomics can help enhance drug safety by identifying genetic variations that increase the risk of

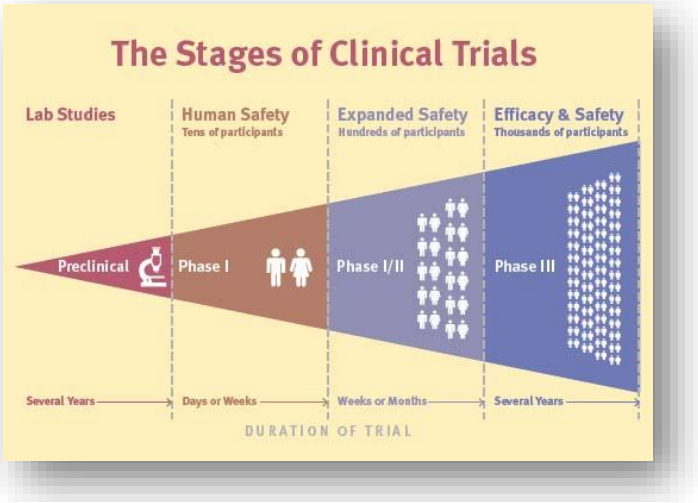

Figure 2: time span of clinical trials and safety

adverse drug reactions. For example, researchers can use genetic testing to identify patients who are at increased risk of developing liver toxicity from certain drugs and then monitor those patients more closely for signs of toxicity. Nutrigenomics can be used in drug screening to identify new drug candidates that target specific genes or pathways involved in disease. In the initial phases of drug discovery, High-throughput screening (HTS) is a commonly used technique.[19] Its purpose is to identify "hit" molecules that display activity against a target of interest from vast compound libraries that may contain thousands of molecules. They can use HTS screening methods to test large libraries of compounds for their ability to modulate gene expression or protein function. It can help identify potential drug-drug interactions based on an individual's genetic makeup. This knowledge can help clinicians avoid prescribing drugs that may interact negatively, reducing the risk of adverse side effects.

3.1 Understanding drug resistance

Nutrigenomics can help understand drug resistance by identifying genetic variations that make tumours or pathogens resistant to drugs. This information can be used to develop new drugs or drug combinations that are more effective against resistant strains. Nutrigenomics can also be used to develop personalized nutrition plans that complement drug therapies. For example, researchers can use genetic testing to identify patients who have a higher risk of developing nutrient deficiencies or who may benefit from specific dietary interventions. Nutrigenomics can be used to develop nutritional supplements that are tailored to an individual's unique genetic makeup. Nutraceuticals are functional foods or dietary supplements that have potential health benefits beyond basic nutrition.[1] Nutrigenomics can be used to identify bioactive compounds in food that may have health-promoting effects, as well as to understand how these compounds interact with genes and metabolic pathways in the body. By leveraging nutrigenomics, it may be possible to develop more targeted and effective nutraceuticals that can be used to prevent or treat specific diseases. For example, a nutraceutical containing a bioactive compound that targets a specific gene or pathway involved in the development of a particular disease could be developed. This approach could potentially provide a safer and more natural alternative to conventional drug therapies.[20]

Drug-food interactions occur when nutritional factors cause changes in a drug or when drug interaction leads to alterations in nutritional or dietary factors. Food-drug interaction as the approach in which nutrients from a specific food interact with a drug when both are taken together, resulting in changes in the drug's pharmacokinetics, bioavailability, therapeutic efficacy, and pharmacodynamics.[2] The authors give examples such as the neutralization of dietary vitamin K from plants with warfarin, leading to pharmacodynamic antagonism, and the bioflavonoid in grapefruit, which blocks an enzyme called CYP3A, leading to slow down of metabolism of many drugs.

Diabetes mellitus (DM) is a set of metabolic diseases caused by defects in insulin secretion, insulin activity, or both, resulting to hyperglycemia. DM is a global burden that causes dysfunction and/or failure of

cardiovascular and excretion systems. According to recent estimates by the International Diabetes Federation 2023 8.3% of adults (382 million individuals) have diabetes, and this number is expected to exceed 592 million within span of 25 years. DM can be classified into type 1(T1) and type 2 (T2) DM.[16] T2DM causes major health issues and a significant economic burden on budgets. Obesity is the risk factor for causing DM compared to individuals with a normal weight.[4] Other risk factors include fast food diets which have replaced conventional diets, including poultry, canned and refined macronutrients, and lipids.[18]

Hyperglycemia and hyperlipidemia are results of Irregular insulin secretion which has been observed in both obesity and T2DM.[21] Studies proposed that regular high intake of sugar and saturated fatty acid can lead to glucolipotoxicity, having negative effect on insulin secretion from the β-cells. Habitual coffee consumption is associated with a significantly reduced risk of T2DM as caffeic acid, chlorogenic acid, and ferulic acid and found in coffee and are associated with DM.

3.2 Drug discovery from natural products; Treatment of neurodegenerative diseases

Using natural products has been proven to be an effective method for discovering new pharmaceuticals. Many drugs that are currently approved were originally derived from natural compounds.[22] The chemical diversity of natural compounds surpasses that of artificially synthesized molecules found in man-made libraries. Natural compounds can associate with and modulate protein targets and may be regarded as an augmented drug-like molecules that have evolved over time. Despite this, in the past two decades, many pharmaceutical companies have reduced or eliminated their natural product discovery programs.[23] Monitoring natural products for pharmacologically active compounds is a formidable task that requires a substantial number of resources. To expedite the screening and recognition of the most promising molecules, innovative approaches are needed at the initial steps of drug discovery pipelines.[24]

Drug discovery from natural products has been an important approach for developing novel therapeutics for various diseases, including neurodegenerative disorders. Cerebral degenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease are specified by the continuous deprivation of neurons and their functions, resulting in cognitive impairment, movement disorders, and other neurological symptoms.[3] One of the major challenges in drug discovery for neurodegenerative diseases is the complexity and heterogeneity of the brain, which makes it difficult to develop drugs that can effectively cross the blood-brain barrier and target specific pathological processes in the brain. In addition, many drugs that show promise in preclinical studies fail to translate to clinical trials, often due to safety and efficacy issues.[23] Natural products have been a rich source of drug for many years, and there are several examples of natural products that have been used in the treatment of neurological disorders. For example, the alkaloid galantamine, derived from the snowdrop plant, is used to treat Alzheimer's disease. Similarly, the drug levodopa, used to treat Parkinson's disease, is a synthetic version of the natural amino acid L-dopa, which is obtained from broad bean plant.[25] Despite the potential of natural products, the discovery and development of new drugs from these sources face several challenges. One of the major issues is the limited availability of natural products, which are often difficult to extract and purify in sufficient quantities for drug development. In addition, natural products often have complex structures that can be challenging to synthesize and modify.[26] Another promising approach is the use of artificial intelligence (AI) and machine learning to screen large libraries of natural products and predict their potential therapeutic activity. These techniques can also be used to optimize the structure of natural products and improve their efficacy and safety profiles.

In conclusion, natural products offer a promising source of drug leads for the treatment of neurodegenerative diseases, but the challenges of discovering and developing new drugs from these sources remain.

However, recent advances in technology and computational methods offer novel solutions to these old problems and pave the way for the discovery of new and effective therapies for these devastating diseases.

3.3 Biomarkers in therapeutic and personalized Medicine

A biomarker is a biological substance that can be cellular, biochemical, molecular, genetic, protein, metabolite, specific post-translational modification, or physiological or physical signs.[27] Biomarkers are generally classified into three categories molecular, imaging, and psychometric. Molecular biomarkers are those that are measured at a molecular level, imaging biomarkers are those that are detected through imaging techniques such as CT scans, while psychometric biomarkers rely on measuring psychological or cognitive changes.[28] The Food and Drug Administration (FDA) pharmacogenomics guidance provides further clarification of biomarker categories, dividing them valid biomarkers based on available scientific information. Clinical endpoint biomarkers reflect how a patient feels, functions, or survives, while surrogate endpoint biomarkers substitute for a clinical endpoint. However, only a few biomarkers are surrogate endpoints, with the HIV 'viral' load being an example.[23]

Nevertheless, recent advances in genomics, transcriptomics, proteomics, metabolomics, cytometry, and imaging, in conjunction with bioinformatics and biostatistics, have made it possible to accelerate the discovery and development of specific biomarkers for complex chronic illnesses. Although many challenges remain, ongoing efforts to discover and develop disease-related biomarkers will improve decision-making throughout drug development and enhance our comprehension of disease processes. Furthermore, effectively translating preclinical biomarkers into clinical practice will pave the way for personalized therapies for complex disease areas, benefiting patients, healthcare providers, and the bio-pharmaceutical industry. Despite significant progress in cancer treatment, the development of personalized chemotherapeutic medications that are both biologically potent and have low cytotoxicity rates remains a significant challenge. However, two promising candidates, porphyran have been identified for their ability to modulate cell death pathways such as apoptosis and autophagy. These substances have the potential to act as a "magic bullet" against cancer cells that do not respond to traditional therapies or are resistant to multiple drugs. Future clinical trials could explore the synergistic effects of combining porphyran or OP with existing chemotherapeutic drugs, providing even greater potency. Not only are they cost-effective, but their selective cytotoxicity also makes them an ideal choice for cancer treatment. Furthermore, utilizing advanced delivery systems such as liposomes, polymers, microemulsions, or nano-carriers could further enhance the targeted delivery of porphyran and OP, improving their efficacy.[29]

Conclusion

In this synthetic review, we have explored the dynamic field of nutrigenomics and its implications for understanding and managing diseases and genetic disorders. Through a comprehensive analysis of current research findings, we have elucidated the intricate interplay between dietary components and genetic variations, shedding light on the mechanisms underlying gene-diet interactions and their impact on health outcomes. Our synthesis highlights the potential of nutrigenomics in personalized medicine, offering insights into tailored dietary interventions based on individual genetic profiles. By leveraging advances in genomic technologies and computational tools, researchers are increasingly able to unravel the complex relationships between diet, genes, and disease susceptibility. These insights have profound implications for disease prevention, treatment, and health promotion, paving the way for more targeted and effective interventions. Looking ahead, the prospects for nutrigenomics are promising. As our understanding of gene-diet interactions continues to evolve, so too will the development of novel therapeutic strategies and personalized nutrition approaches. Integrating nutrigenomic principles into clinical practice holds the potential to revolutionize healthcare delivery, enabling

more precise risk assessment, diagnosis, and treatment selection. Furthermore, the translation of nutrigenomics research into public health policies and guidelines has the potential to promote population-wide health benefits and reduce the burden of chronic diseases.

In conclusion, nutrigenomics represents a paradigm shift in our approach to health and disease, offering a pathway towards more personalized and effective interventions. By harnessing the power of nutrigenomics, we can unlock the full potential of nutrition in promoting health and mitigating the risk of diseases, ultimately improving the well-being of individuals and populations worldwide.

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