Review Article

Nutritional Proteomics: A Key to Unlocking Optimal Human Health

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Abstract

Proteomics is a scientific field dedicated to the investigation of protein structure function and interactions within living organisms. The review paper explores facets of proteomics and its diverse applications across various research domains. The review sheds light on the crucial role of the proteome within an organism, influenced by factors such as its physiological condition and surroundings. Nutritional proteomics, referred to as neuroproteomics, employs proteomic methods to delve into the interactions between proteins and bioactive components found in food. Nutriproteomics and nutrigenomics, enable comprehensive investigations into how nutrients and proteins interact and impact the human proteome and genome. The review highlights the exploration of proteome alterations associated with diseases and emphasizes the role of nutritional proteomics in disease treatment. It accentuates the potential of proteomics in identifying biomarkers for diseases and unraveling intricate protein-level alterations associated with various conditions, such as infectious diseases, cancer, cardiovascular disorders, and neurodegenerative illnesses. The connection between proteomic technologies for drug discovery is also discussed. The review further underscores how the integration of different 'omics' disciplines offers a holistic understanding of complex biological systems. Ultimately, the review concludes by emphasizing the promising role of proteomic technologies in advancing both research and healthcare.

Keywords: Proteomic, Nutritional proteomics, Omics, Disease-associated proteome, Biomarkers

Introduction

Definition of Nutritional Proteomics

The composition of proteins in an organism, known as the proteome, varies in function depending on its location within the tissue, the organism's physiological state, and its surrounding environment. It is a critical component because it holds information about post-transcriptional and post-translational regulation of protein expression, as well as information on gene expression. As a result, proteomics can be used to map an organism's adaptive potential and provide a current snapshot of its state [1].

Recent advancements in omic technologies have allowed for the study of proteomes and peptidomes in different species. This has facilitated the creation of protein databases that can be utilized for protein identification, gene ontology, and phylogenetic comparisons through homology-based methods [2].

In the last decade, proteomics has made significant progress in terms of its development and utilization. It has become a valuable tool in various clinical and health sciences applications, such as food science, biomarker research, and identification of drug targets. Proteomic studies have led to the discovery of biomarkers for a range of diseases, including cancer, cardiovascular disease, AIDS, and renal disease, through the use of body fluids like serum and urine [3].

Nutritional proteomics, also known as neuroproteomics, involves applying proteomic techniques to research related to nutrition. The interaction between proteins and bioactive food components can occur in two distinct ways, the first aspect, involves examining how nutrients influence protein expression, which can be tracked through protein mapping. Secondly, nutrients interact with proteins through post-translational modifications or interactions with small molecules. These interactions lead to alterations in the three-dimensional configuration of these affected proteins [4].

The combination of nutritional, genomics, and proteomics fields in the postgenomic period has resulted in the emergence of neuroproteomics and nutrigenomics. These disciplines focus on studying the interaction between

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nutrients and the human proteome and genome. Further advancements in other omics fields, including metabolomics, interactomics, and microbiomics, are anticipated to enhance the understanding of nutrition and its underlying components [5].

Proteomics comprises six categories, as delineated by Carbonaro [6]. Functional proteomics, expression proteomics, investigating protein-protein interactions, proteome mining, exploring posttranslational modifications, and delving into structural proteomics [7]. Functional proteomics explores protein functions and interactions, shedding light on molecular mechanisms and uncharacterized proteins. Expression proteomics explores changes in protein expression, both quantitatively and qualitatively. In addition, protein-protein interaction studies unravel intricate cellular pathways through in vitro, in vivo, and silico methods, aided by computational predictions and machine learning. Furthermore, structural proteomics provides insights into the 3D protein structure, interactions, and therapeutic implications. On top of that post-translational modifications control protein signaling, stability, localization, and interactions. Ultimately, proteome mining investigates proteins holistically, offering disease-related, functional, and domain-based classifications, including chemical proteome mining **(Figure 1)** [6, 8-12].

Proteomics has found new applications in the fields of neuroproteomics and food comics, allowing for the study of the relationship between food and health. The use of proteomics-based techniques is becoming a promising tool in nutritional studies for understanding the links between food and disease [13].

Nutriproteomics and foodomics utilize proteomics-based techniques to study how dietary nutrients, functional foods, and nutraceuticals affect protein expression. With the growing use of these components in both humans and animals, it is crucial to understand their impact on health and disease outcomes. Therefore, it is necessary to identify bioactive proteins, discover biomarkers that are important for disease control, and evaluate the safety of existing and novel nutraceuticals to improve health outcomes [13].

Nutritional Proteomics: Current Techniques and Approaches

Omics technologies such as genomics, transcriptomics, proteomics, and metabolomics are allowing personalized medicine to be practiced at an extremely detailed molecular level. While each of these technologies has brought about medical advancements that have already entered clinical practice, individually, they cannot fully understand the complex nature of most human diseases. Therefore, combining multiple omics technologies has become an approach to gaining a more comprehensive understanding of biology and disease [14].

The production and consumption of food are undergoing significant changes worldwide, and consumers are increasingly conscious of the food they eat. As a result, there is a growing interest in the field of foodomics, which involves using advanced omics methods to study food [15]. Foodomics encompasses a range of methods including epigenetics, transcriptomics, metabolomics, proteomics, peptidomics, and genomics to explore aspects like food safety, quality, traceability, and the identification of novel bioactive elements in food [16]. Among these approaches, proteomics is extensively applied in contemporary food studies [17].

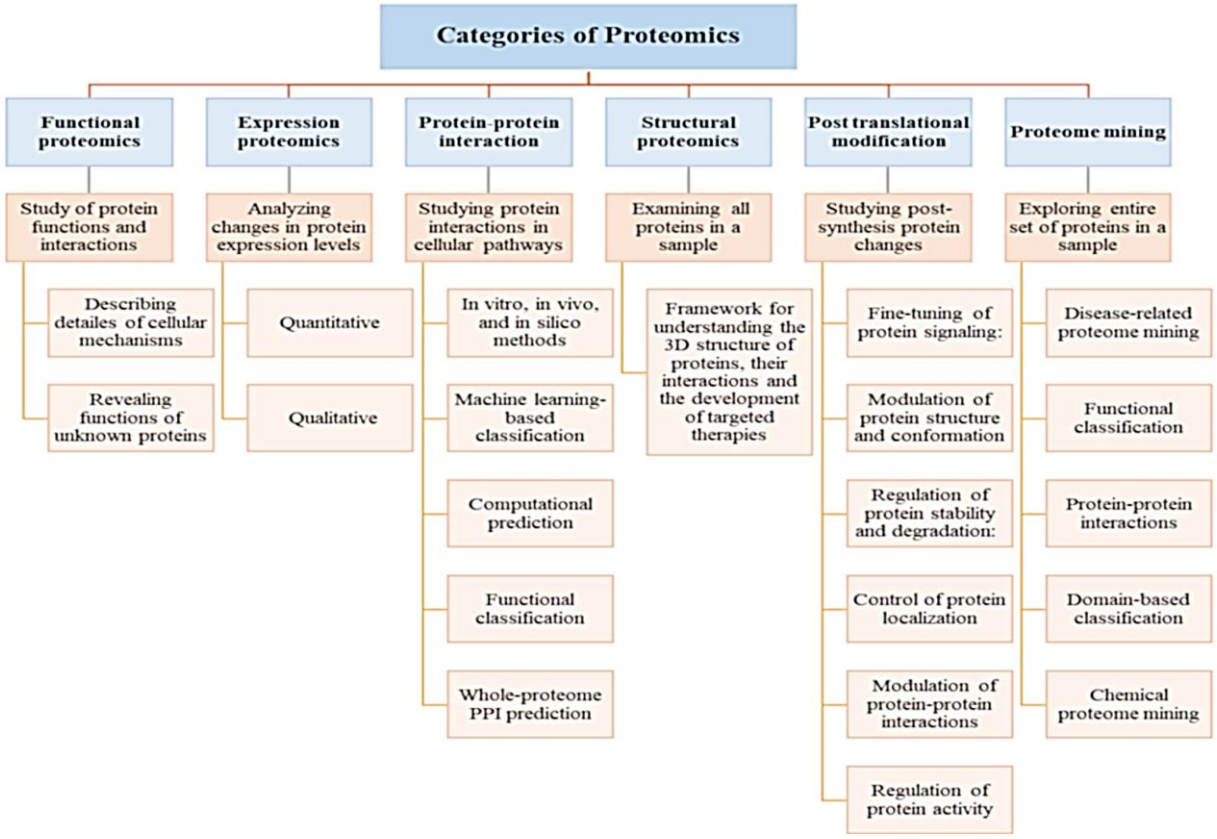

Figure 1. Categories of Proteomics. This diagram illustrates the diverse empires within proteomics research, encompassing various approaches and focuses. PPI is protein-protein interaction. The content within the Figure was derived from [6, 8-12].

Proteomics has the potential to examine food quality, and this can be improved by enhancing the techniques used in food production [18]. The safety of food is a critical health issue, and numerous individuals worldwide experience different types of foodborne diseases each year [19]. It can also assess an individual's response to different dietary interventions. By analyzing protein expression changes in response to specific diets, investigators can identify proteins or protein pathways that are modulated by dietary factors. This information can help determine the effectiveness of different dietary approaches in managing diseases and guide the selection of personalized nutrition plans that are most likely to yield positive outcomes for individuals based on their protein expression profiles [20].

The operational basis of proteomics includes key phases: (i) extraction of proteins, (ii) separation and quantification of proteins or peptides, (iii) identification of proteins, and (iv) analysis and interpretation of the obtained data [8]. The process of extracting proteins is performed from the sample designated for analysis [21]. Protein separation is achieved using the two-dimensional gel electrophoresis (2D-PAGE) method. These separation techniques are applied in both the bottom-up proteomic approach and the top-down approach [22].

The top-down mass spectrometer (MS) technique, facilitates a comprehensive exploration of protein modifications and functions. The development of high-resolution mass spectrometers, liquid chromatography separation, and data analysis software has led to the increasing popularity of top-down proteomics. By employing top-down mass spectrometry (MS), researchers have pinpointed distinct protein variations, known as proteoforms, that display noteworthy variations in biological function when compared to similar proteoforms. Nevertheless, merely qualitatively identifying proteoforms might not be enough to ascertain their biological importance. To delve deeper into the distinctions in biological functions among these protein proteoforms, scientists have devised quantitative top-down MS techniques. These methods empower researchers to scrutinize proteomes at the proteoform level, as opposed to the peptide level [23].

The majority of proteomic investigations utilize proteases to break down proteins into peptides, following a predetermined structure. Subsequently, these peptides undergo analysis within an MS/MS instrument, where their mass-to-charge ratio and anticipated sequence are connected to derive insights about the proteins within the sample. All experimental arrangements that commence by analyzing peptides resulting from complete protein digestion and rely

on a protein database to attribute these peptides to their source open-reading frame are collectively categorized as "bottom-up" proteomics [24].

MS has demonstrated its effectiveness in characterizing proteins and analyzing complicated protein samples [25]. Various MS approaches have been developed for probing the proteome, such as surface-enhanced laser desorption ionization (SELDI) [26], matrix-assisted laser desorption ionization (MALDI) [27] joined with time-of-flight (TOF) or other devices, as well as gas chromatography MS (GC-MS) or liquid chromatography MS (LC-MS). GC-MS or LC-MS permits the online separation of intricate samples, making them more commonly employed in high-throughput quantitative proteomics [28].

To detect and recognize a protein using proteomic assays, the protein must exist in the database library. Commercially available peptide fingerprint libraries, such as "spectra bank," have mass spectral fingerprints of various pathogenic bacteria species and major spoilage-causing species found in seafood. This particular library is composed of 120 species relevant to the food sector [21]. Techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry/ liquid chromatography-mass spectrometry (MS/LC-MS) can be utilized for proteomic analysis to identify allergens and toxins present in food [29].

Chromatographic separation methods such as ultra-high performance liquid chromatography (UHPLC) along with advancements in MS hardware, have significantly improved since the beginning of the 21st century. These advancements have permitted the transition from gel-based to chromatography-based proteomics, which involves label-free or label-assisted techniques for quantitation. Most methods involve separating and quantifying at the peptide level. To achieve this, protein samples of high complexity undergo a process of denaturation followed by enzymatic digestion, and the resulting mixture of peptides is separated via one or two dimensions of LC (2D-LC) [29].

Nutritional Proteomics in Disease Prevention

Proteomics can be used to identify biomarkers for disease prevention. Biomarkers are signals within our biology that indicate the presence of particular disorders. There are various types of biomarkers worldwide, but the most frequently used ones include microRNAs, inflammatory markers, adipocytokines, oxidative stress, gut microbiota, nutrient levels, and blood cell characteristics. The early detection of biomarkers is often related to metabolic disease or syndrome, making the identification of these miRNAs a valuable approach to diagnosis and prevention. For example, markers including microRNA, adipocytes, oxidative stress, blood cell profile, nutrients, and microbiota, show potential in detecting obesity. Due to the wide-ranging effects of obesity, it is necessary to implement a comprehensive prevention strategy that takes into account multiple dimensions in all countries [30].

Omic technologies have enabled the identification of biomarkers and understanding of the molecular mechanisms of diseases in a nutrient-specific manner [31]. Common nutritional biomarkers include albumin, prealbumin, transferrin, and CRP, but their use as accurate nutritional biomarkers has been criticized due to poor correlation with nutritional status [32].

Other factors can alter biomarker levels, such as inflammation, hydration, and zinc deficiency. Despite these limitations, nutritional biomarkers remain useful in the clinic, and ongoing research is exploring new biomarkers using omic technologies. However, the use of omic biomarkers as an effective, affordable, and simple personalized nutrition tool is still challenging due to the complexity of metabolic regulation and various technical and economic constraints [33]. The unreliability of nutritional biomarkers is a significant issue in the field. As a result, it is crucial to find a dependable and highly detectable nutritional biomarker. Antibody-based techniques, particularly enzyme-linked immunosorbent assays (ELISA), are typically used to validate protein biomarkers in clinical assays [34].

Personalized nutrition plans utilizing nutritional proteomics enable the creation of individualized nutrition plans that cater to precise dietary requirements, enhancing nutrient intake for the prevention and management of diseases. By merging insights from nutritional proteomic analysis with other -omics disciplines, researchers can formulate all-encompassing personalized nutrition strategies, meticulously catering to specific nutritional needs and optimizing nutrient intake for disease prevention and treatment [35].

Regarding disease management, nutritional proteomics has the potential to pinpoint proteins or protein pathways influenced by dietary elements, linked to conditions such as cancer **(Figure 2)**. This knowledge can be harnessed to devise dietary interventions that effectively control cancer and enhance patient outcomes [36].

Exploring Disease-Associated Proteome Changes

Proteins serve as intermediary traits for diseases and offer an understanding of the mechanistic connection between genetic and non-genetic risk factors and their impact on clinical results. Linking protein levels with DNA sequence variations that align with risk alleles for prevalent illnesses can unveil pathways linked to these diseases, thereby identifying potential new targets for drugs and informative biomarkers for translational applications [37]. It has been proposed by Keijer *et al*. [38] that personalized nutrition has gained significant attention as a means of empowering consumers to improve dietary behavior, optimize health, and prevent diet-related diseases. Omics technologies provide detailed assessments of metabolic dynamics, but their translation into

affordable and simple personalized nutrition protocols remains difficult due to metabolic regulation complexity and technical and economic constraints [38]. Proteomics can play a significant role in identifying proteins that have the potential to function as biomarkers associated with disease progression. **Table 1** represents examples of proteins known as biomarkers in various human diseases.

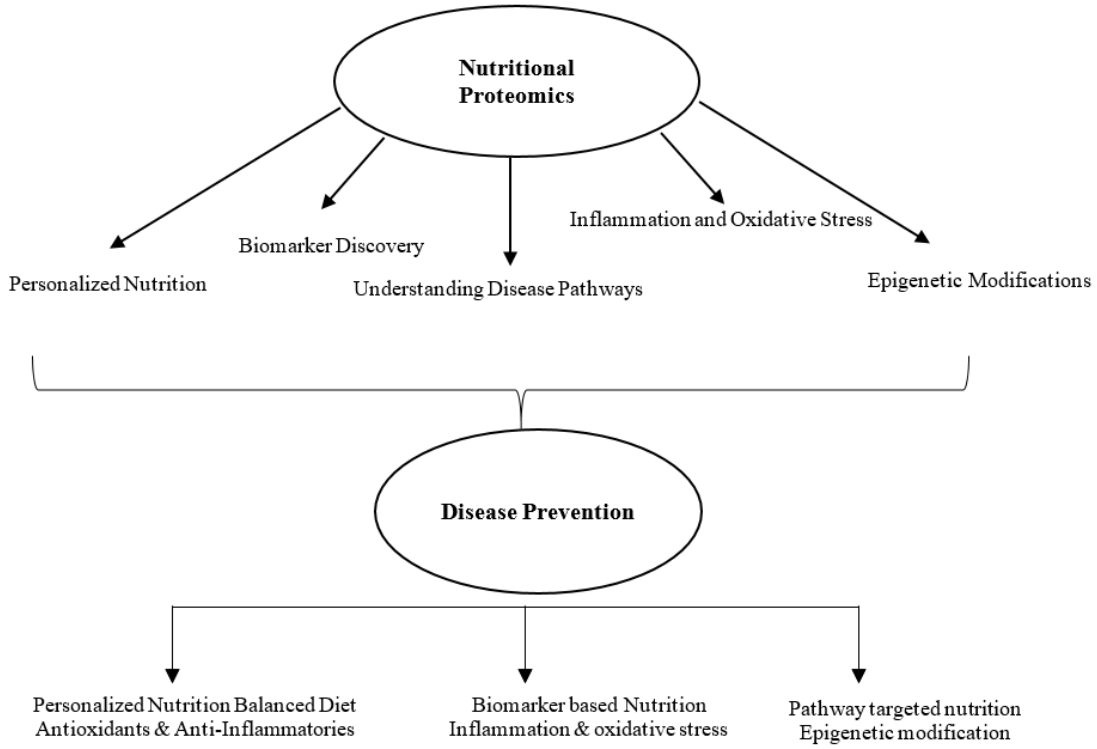

Figure 2. The Intersection of Nutritional Proteomics and Disease Prevention

Table 1. Compilation of Proteins Biomarkers in Several Human Diseases

Protein Potential biomarkers	Human disease condition	References
Hemoglobin A1c	Long-term glucose control in diabetes	[39]
Haptoglobin	Hemolytic anemia or other conditions involving red blood cell breakdown	[40]
CA 72-4	Gastric cancer	[41]
p53	Lung, colorectal, and ovarian cancers	[42]
Myoglobin	Signal muscle damage, such as in cases of heart attack or muscle injuries	[43]
Procalcitonin	The presence of bacterial infections	[44]
S100 Protein	Indicative of certain types of skin cancer, such as melanoma	[45]
Troponin	Diagnosing heart attacks	[46]
Cystatin C	Kidney function	[47]
Cystic Fibrosis Transmembrane Conductance Regulator	Cystic fibrosis	[48]
Bence Jones protein	Multiple myeloma, a type of blood cancer	[49]
Prostate-specific antigen	Prostate cancer	[50]
Human Epidermal Growth Factor Receptor	Breast cancer	[51]
Brain natriuretic peptide N-terminal fragment of the prohormone	Heart failure	[52]

Once these biomarkers are identified through a mass spectrometry-based approach, they require further processing through bioinformatics analyses and validation in diverse populations [53].

Cancer

Proteomics has been used to identify protein biomarkers that can assist in the early recognition of various cancers, such as breast cancer [54]. Limited understanding remains regarding the effectiveness of cancer prevention methods centered around dietary components. Adjustments in nutrient intake involve the intricate modulation of numerous protein networks encompassing factors like transcription, histone modification, enzymes, translation regulators, receptors, and secreted proteins. Nonetheless, employing conventional protein analysis techniques to comprehensively quantify and assess the quality of all proteins governing cancer-related pathways is not feasible [36].

Nutrigenetics explores how specific variations in our genes can impact and be impacted by the nutrients we consume [55]. This predictive knowledge about how nutrients and our genes interact holds the potential to blend nutrition with personalized medicine, taking us a step closer to tailoring cancer treatments to individual needs. This comes from the power of certain nutrients to activate precise mechanisms that delay cancer, aiming at important factors such as apoptosis and deterring angiogenesis, crucial in cancer's growth [56].

Among the various lifestyle optimizations, nutrition has been identified as a key factor that plays a vital role in cancer initiation, progression, and metastasis [57].

Studies have shown that incorporating nutritional interventions, such as fasting in conjunction with standard treatments can enhance treatment efficacy in cancer patients. Scientists are exploring the inner workings of fasting through the lens of genomics, and nutrigenomics offers a way to translate the complex molecular pathways of fasting. Moreover, nutrigenomics can help pinpoint potential biomarkers that could guide nutritional strategies in the context of cancer therapy. This involves conducting detailed quantitative proteomic investigations on both cancerous cells and animal models [57].

The researchers believe that implementing nutritional interventions in clinical settings has the potential to augment existing chemotherapeutic regimes and significantly improve chemotherapy outcomes for cancer patients. Nutrigenomics can explore the connection between nutrients we consume and gene expression. It provides a way to grasp the molecular consequences of dietary limitations, involving the analysis of proteins, shedding light on the intricate interactions between our diet and our genes. Proteomics has not been fully utilized to comprehend nutritional involvement in cancer [57].

A study made by Zhou *et al*. [58] suggested a possibility for future cancer proteomic research on a larger scale, which can help in discovering possible cancer biomarkers and finding new treatment strategies. According to Zhou *et al*. [58], it is crucial to understand the molecular abnormalities in cancers through proteomic characterization. However, traditional methods for profiling an extensive collection of cancer specimens have limitations. The authors conducted a comprehensive study of 16 major forms of human cancer. They analyzed 126 primary tumor tissues, 94 tumor-adjacent normal tissues, and 12 normal tissues using a cutting-edge mass spectrometry-based approach. In their research, they successfully identified a total of 8,527 proteins across various cancer types, encompassing brain, head and neck, breast, lung, esophagus, stomach, pancreas, liver, colon, kidney, bladder, prostate, uterus, and ovary cancers.

Their approach allowed them to pinpoint 2,458 tissue-specific proteins, shedding light on the unique characteristics of each tissue type. Furthermore, they made noteworthy discoveries, identifying proteins that are consistently expressed across all tissues, as well as proteins that are specific to certain tissues and cancer types. Among these findings were 1,139 proteins with therapeutic potential and 21 cancer/testis antigens, offering promising insights into potential targets for cancer treatment and diagnosis [58].

Many laboratory studies have demonstrated that specific dietary elements can function as inhibitors of cancer, but there remains ambiguity regarding whether these nutrients have pro-carcinogenic or anti-carcinogenic properties. Despite a considerable volume of preclinical investigations and clinical trials, most of them only exhibit marginally significant effects [59].

To assess the impact of nutrients on cancer, a connection can be established by examining their interaction with the hallmarks of cancer through their molecular mediators. The hallmark most profoundly influenced is inflammation promoted by tumors, primarily driven by oxidative stress induced by reactive oxygen species [60].

Another example of cancer is oral cancer which is thought to be prevented by maintaining proper oral hygiene, refraining from tobacco and alcohol use, and following a well-balanced, healthy diet. All of these can notably lower the chances of oral cancer, particularly considering the significant role of environmental exposure [61]. The advantageous impact of a diet abundant in vegetables and fruits was demonstrated by many researchers, showing a reduced risk of oral cavity and head and neck cancers. This was especially prominent among individuals who were smokers and alcohol consumers, both of whom typically have an elevated risk for oral cancer [62]. It is widely known that dietary elements can potentially act as catalysts for malignancy. Additionally, certain studies suggest that particular nutrients or components of our diet such as ketogenic diet might have the capability to reduce the likelihood of cells transforming into malignant forms or even delay the growth and metastasis of existing malignant masses [63]. In a preliminary study, serum proteomics without

labeling was applied to examine the quantitative serum proteomic profiles of 13 patients with confirmed oral squamous cell carcinoma and 12 healthy control subjects [64]. The outcomes of the investigation demonstrated the ability to distinguish between oral squamous cell carcinoma patients and healthy individuals based on their respective serum proteomic profiles [64].

Breast cancer remains a prominent contributor to mortality [65], causing an escalated incidence of up to 1,960,681 cases and accounting for 17,708,600 disability-adjusted life years (DALYs) in 2017 [66]. Nutrigenomics was expected to play an essential role in breast cancer prevention and early detection. It was predicted that unraveling the intricate link between nutrition, breast cancer occurrence in infrequent cases, and individuals with gene mutations will yield essential insights for proactive breast cancer management [67]. The information on breast cancer is profound, encompassing epidemiological, societal, and economic dimensions. The complicated relationship between breast cancer and dietary habits is complex, with multifaceted interactions, and non-linearity. Traditional nutritional epidemiological investigations have presented divergent outcomes, with only a marginal correlation observed between diet and breast cancer risk (except for alcohol consumption). Breast cancer is indicated by its multi-dimensional and heterogeneous nature. Histological and, more recently, molecular classifications have shed light on this complex landscape [5].

By utilizing proteomic analysis, proteins that are disrupted in breast cancer have been discovered. This approach has provided insights into how these proteins contribute to the molecular aspects of breast cancer development and progression [68]. In addition, the application of proteomics to biomarker profiling has successfully identified potential biomarkers for breast cancer diagnosis, outcome prediction, and treatment. These biomarkers are pivotal for distinguishing between breast cancer patients and healthy individuals, as well as for predicting patient outcomes [68].

Furthermore, breast cancer has been comprehensively investigated through high-throughput proteomic analysis of formalin-fixed paraffin-embedded tissue. This analysis has yielded valuable knowledge about the molecular changes connected to breast cancer and has offered important information for prognostic evaluation based on the tumor, node, and metastasis (TNM) classification system [69]. Moreover, tear proteome analysis has also played a significant role by enabling the comparison of protein levels between breast cancer patients and healthy controls. This approach has illuminated the molecular alterations associated with breast cancer and has even provided potential biomarkers for early detection and diagnosis [70].

MS-based proteomics methodologies, including top-down, middle-down, and bottom-up approaches, supplement conventional histopathological analysis by simultaneously investigating the expression, modification, and interaction of numerous proteins. These MS-based proteomics procedures, such as LC-MS/MS, MALDI-TOF MS, SELDI-TOF MS, MALDI-TOF/TOF MS, and MALDI MSI, work in synergy with established pathological techniques. They enable the assessment of protein expression levels, modifications, and interactions. The identification of dysregulated proteins using proteomics is essential for various purposes in the context of breast cancer. Such as uncovering novel biomarkers, assembling groups of biomarkers to facilitate early diagnosis and accurate differentiation and characterization between breast cancer subtypes, quantifying post-translational modifications and abnormal PPI, precise diagnoses and prognostic insights, and mechanisms through which dysregulated proteins contribute to breast tumor initiation, invasion, and resistance to treatment [68].

Natural compounds such as vitamins C, D, E, B, K, A, and selenium are gaining recognition for their potential role in fighting cancer [71]. These substances are now being identified as significant elements in cancer prevention and inhibition. Although their impact doesn't necessarily directly relate to inducing cancer cell apoptosis, the consumption of vitamins or other molecules from various food sources or synthesized drugs is undergoing comprehensive exploration through advanced technologies in oncology. Consequently, any deficiency in the aforementioned nutrients has been linked to the development of numerous cancers, and understanding their genetic makeup can yield valuable insights into underlying mechanisms and pathways. This intricate biological influence can be comprehended using approaches from systems biology. Specifically, the optimal dosage of these micronutrients can be assessed to maximize their favorable effects [72].

Overall, the realm of neuroproteomics has substantially enriched our understanding of the molecular mechanisms related to breast cancer and has uncovered potential biomarkers for early detection and diagnosis. These insights originating from neuroproteomics hold promise for enhancing patient outcomes and mitigating the impact of this disease [68].

Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) used to be viewed as a concern primarily in developed nations, but it has become a global issue [73]. The lack of ability to identify early-stage atherosclerosis was a significant obstacle in applying individualized treatments to prevent coronary heart disease. Having a detailed comprehension of the arterial protein networks and their transformations during the initial stages of atherosclerosis could lead to the discovery of fresh biomarkers for disease detection and better targets for therapy [74].

Researchers investigated proteins found in human coronary and aortic tissues. Their study pinpointed specific proteins-protein networks, and regulatory frameworks that differed between the two arterial beds or were indicative of early-stage

atherosclerosis. The research also showcased that the proteins uncovered via tissue proteomics could be harnessed to develop useful plasma biomarker tests that hold direct clinical significance. The findings of the study offer valuable resources that could pave the way for upcoming research on human arterial protein biology. There is a considerable difference in the appearance of mitochondrial proteins in normal arterial samples, which suggests that coronary arteries have a greater aerobic capacity than the distal aorta. Also, there was a significant difference in mitochondrial protein mass between coronary and aortic tissues in humans [74]. Progress in high-throughput plasma proteomics, when coupled with automated learning strategies, has the potential to open up fresh avenues for enhancing the categorization of risk in patients with atherosclerotic cardiovascular disease (ASCVD) [75].

Group of researchers performed research on enhanced cardiovascular risk prediction using targeted plasma proteomics in primary prevention. The study involved comparing a risk model based on protein levels with a model based on traditional risk factors for forecasting cardiovascular procedures in the primary prevention setting of the European Prospective Investigation (EPIC)-Norfolk study. This was followed by validation of the findings in the Progression della Lesione Intimale Carotidea (PLIC) cohort. The outcomes showed that in a primary prevention setting, the proteome-based model was more effective than the model based on clinical risk factors for predicting the risk of cardiovascular disease events. However, researchers suggest that further authentication in a large prospective primary prevention cohort is necessary to assess the model's value for future clinical use in preventing cardiovascular diseases [76].

Through the application of a proteomic platform pinpointing 85 significant proteins related to cardiovascular disease, researchers have successfully identified distinct biomarkers linked to different cardiovascular outcomes. Specifically, eight biomarkers were linked with incident ASCVD, 18 with incident heart failure (HF), 38 with all-cause mortality, and 35 with cardiovascular disease death. This identification took into account potential clinical factors that might confound the results. Employing a comprehensive approach considering various markers alongside clinical factors, growth differentiation factor (GDF)15 was found to be connected with all results [77].

Furthermore, N-terminal pro-b-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), and leptin exhibited associations with incident HF. Within a multimarker model, C-type lectin domain family 3 member B (CLEC3B or tetranectin), arabinogalactan protein 1 (AGP1), soluble receptor for advanced glycation end products (sRAGE), peripheral myelin protein 2 (PMP2), uncarboxylated matrix Gla protein (UCMGP), kallikrein B1 (KLKB1), insulin-like growth factor binding protein 2 (IGFBP2), insulin-like growth factor 1 (IGF1), leptin receptor, and cystatin-C were all linked to total death rates [77].

These findings reveal multiple novel associations between protein biomarkers regulating metabolic and inflammatory pathways and clinical outcomes, facilitated by a high-throughput, multiplexed discovery proteomic platform. Essentially, the scientists utilized this focused strategy to build on current findings, discover connections between biomarkers and occurrences of CVD, and confirm prior genetic correlations [77].

Neurodegenerative Diseases

Neurodegenerative diseases are usually diagnosed based on clinical symptoms and neuroimaging. These diseases are clinically diverse and can reflect various neurodegenerative processes with complex pathologies and variations among patients. Recent research has shown that different pathologies can produce similar clinical symptoms, making accurate diagnosis even more difficult [78]. Researching neurodegenerative diseases can uncover and measure particular metabolites and proteins that contribute to cellular pathways. This knowledge can then be applied to develop therapeutic strategies that aim to stop or even reverse the progression of these conditions [78].

Neurodegenerative diseases are marked by the irregular buildup of aggregated proteins in the brain. Andrews *et al*. [78] conducted in vivo pulse isotope labeling to examine alterations in protein turnover and abundance across several mouse models of neurodegeneration. Their findings indicate that pathological tissue in the disease state is characterized by an overall rise in protein turnover and repair at the proteome level. Conversely, in normal wild-type mice, the aging process in the mammalian brain is linked to a widespread deceleration in protein turnover [79]. The levels of a specific protein in the brain depend on the rates of its synthesis and degradation, which are regulated by distinct cellular mechanisms. To simultaneously measure both protein flux and abundance in mouse models of neurodegeneration, the researchers used metabolic labeling in live mice along with global proteomic profiling. Their method allowed them to differentiate changes in protein expression caused by synthesis from those resulting from degradation. They found that protein turnover increases were linked to greater pathology in several models. This straightforward multidimensional approach facilitates a comprehensive analysis of proteome dynamics and enables the identification of affected proteins in live animal testing, including disease models [79].

Dementia is a very common brain disorder in older people, but there is currently no known cure. New techniques in proteomics could help to discover changes in the brain's proteome that could provide insight into the causes of the disease and identify specific proteins that could be developed as biomarkers. Proteomics research was conducted on the brains of individuals affected by Alzheimer’s disease, Parkinson's disease dementia, frontotemporal dementia, and amyotrophic lateral sclerosis. These researches validate previous knowledge about changes at the cellular level and

also found new proteins that could be linked to different aspects of these diseases [66].

Several dementias are designated as proteinopathies [66]. Proteomics has the capability of detecting abnormal protein expression in the brain of dementia patients, but its implementation has been limited by several factors including the complicated nature of the disease, individual differences between patients, and the lack of available high-quality brain tissues. However, technological advancements in mass spectrometry have facilitated the detection of the entire tissue/cell proteome in a shorter time [80] and with only a small number of clinically relevant human samples [66].

Parkinson's disease dementia (PDD) is a common neurodegenerative disease. It affects 2-3% of the population older than 65, while dementia with Lewy bodies (DLB) constitutes 15-20% of late-onset dementias [81]. Patients with PDD often suffer from mild memory loss and motor symptoms due to the accumulation of Lewy bodies, α-synuclein (SNCA) positive inclusions in the substantia nigra. The origin of the illness is not completely comprehended but is believed to be due to a complex interplay of genetic and environmental factors. Early-onset Parkinson's disease is infrequent, however, several mutations can cause it [81].

The origins and varied clinical manifestations of PD have been examined through molecular, pathophysiological, and clinical lenses. The utilization of high-throughput proteomic analysis on cerebrospinal fluid (CSF) has presented novel paths for exploring this diversity [82]. Variances in the proteome between individuals with idiopathic conditions and control subjects imply heightened neuroinflammation, potential neuroprotection facilitated by vasoactive compounds, and perturbations in iron metabolism and mitochondrial function/oxidative stress. Additionally, leveraging proteomic data allowed researchers to categorize idiopathic patients into distinct "endotypes." These recognized endotypes showcase dissimilarities in the progression of cognitive and motor impairments, aligned with established protein-based risk assessments [82].

Alzheimer's disease is the known common form of dementia among neurodegenerative diseases which is characterized by the accumulation of β-amyloid protein (Aβ) in the extracellular matrix and intracellular neurofibrillary tangles. Numerous studies utilizing quantitative proteomics platforms have been conducted on brain, CSF, plasma, and animal models of Alzheimer's disease. Jain and Sathe performed MS-based proteomics investigations on AD and provided a brief overview of the discovery and validation stages involved in identifying candidate biomarkers [83].

Proteomics can be used to analyze the proteome of biological samples, with the bottom-up approach being the most commonly used method. This involves liquid chromatography joined with tandem mass spectrometry to identify and quantify peptides from digested proteins. Recent studies have been successful in quantifying over 2000 proteins, leading to the identification of significant changes in molecular pathways within the brains of individuals affected by disease [84, 85]. There are two key quantitative proteomics methods label-free data-dependent acquisition and isobaric multiplex labeling strategies using iTRAQ or TMT reagents [84].

Infectious Diseases

Proteomics has been used to identify changes in the proteome associated with infectious diseases, including viral infections such as HIV and hepatitis C, and bacterial infections such as tuberculosis. Approximately a quarter of global deaths are attributed to infectious diseases, such as HIV/AIDS, lower respiratory bacterial infections, and malaria [86].

Protein assessment and analysis of proteins associated with infectious diseases have been facilitated by proteomics research, making it a valuable tool [87]. Proteomic profiles of a specific organism, tissue, or cell are influenced by various environmental factors, such as those caused by infectious diseases [87]. In the study of infectious disorders, proteomics has been applied to investigate their pathogenesis, etiology, and pathology [87]. Additionally, proteomics approaches have proven useful in identifying pathogens, emerging and re-emerging infectious agents, and in understanding their pathogenesis [88]. The constant interaction between hosts and pathogens is an important aspect of studying infectious diseases, and proteomics has been employed as a powerful tool to explore this area [89].

Advancements in genetic, analytical, molecular, and imaging techniques have benefited the field of microbiology in the past century. There has been an increase in the use of MS and proteomics-based technologies to study pathogen-host interactions and gain insights into the biological basis of infectious diseases [90]. Greco and Cristea provided a perception of the role of MS-based proteomics in characterizing the molecular structure and composition of viral and bacterial pathogens and their interactions with hosts in both space and time. They highlighted the contribution of MS-based proteomics in supporting the development of diagnostics and therapies, as well as the emerging role of multi-omics approaches in providing a systems biology view of pathogen-host relationships [91]. HIV/AIDS, tuberculosis, malaria, measles, and hepatitis, have been extensively studied through proteome research, and the majority of infectious disease-related fatalities can be attributed to a relatively small number of pathogens [87].

Proteomics is commonly employed to ascertain expression patterns in response to particular stimuli during specific timeframes. The quest involves accurately determining the shapes and biological functions of proteins, which ultimately govern a wide range of cellular processes [87]. Proteomic exploration is frequently more appropriate than DNA microarray analysis for examining alterations in gene expression patterns when responding to specific

circumstances, including a health disorder or the presence of a specific pathogen. Proteomic studies have examined serum samples related to hepatitis, revealing consistently low levels of Apolipoprotein A1 (ApoA1) isoform and the C-terminal portion of complement factor C3 in hepatitis B virus-positive individuals (HBV) with hepatocellular carcinoma (HCC) compared to healthy participants, who exhibited higher mean values with significant variability. HBV mice also displayed elevated levels of fatty acid binding protein 5 and acyl-CoA binding protein in their livers compared to wild-type mice. Immunoblotting analysis by using 2D-gels of proteins from cell culture lysates and liver tumors has been used to identify potential serum autoantibody biomarkers for chronic hepatitis C or hepatitis C virus (HCV)-HCC. Additionally, the impact of HCV infection therapies on serum protein levels has been investigated, revealing significant alterations in cytoskeletal proteins, molecular chaperones, heat shock proteins (HSP70 family and HSP60), metabolic enzymes (such as glutamine synthetase), enzymes participating in glycolysis, and urea cycle in patients. Proteomics has also been used to identify novel biomarkers for diagnosing mycobacterium tuberculosis infection [87].

The proteomes of various bacteria and viruses causing lower respiratory tract infections have been studied, which can aid in identifying new antigens for vaccine development and enhancing our understanding of pathophysiology. For instance, two-dimensional electrophoresis (2DE) and two-dimensional semipreparative electrophoresis (2DPE) combined with MS and tandem MS have been utilized to identify potential vaccine candidates in nontypable haemophilus influenzae, a gram-negative bacterium responsible for conditions like acute otitis media, sinusitis, and community-acquired pneumonia. Shotgun proteomics is now employed to study the proteome of diverse lifecycle stages by detecting peptide mass fingerprints, as demonstrated in a significant proteomic investigation of malaria parasites, specifically Plasmodium falciparum, and its various lifecycle phases [87].

A multiplexed proteomics assay was introduced that enables the valuation of disease severity and prognosis in COVID-19. This assay measures the levels of 50 peptides, derived from a combination of 30 established and newly identified COVID-19-related protein markers, in a single analysis using standard laboratory techniques such as analytical flow rate liquid chromatography and multiple reaction monitoring (LC-MRM). The researchers performed two experimental studies on COVID-19 patients to validate the assay. The assay successfully distinguished between healthy subjects, mild, moderate, and severe COVID-19 infections in both studies, capturing both the characteristics of infection and severity [92].

Proteomic datasets have consistently demonstrated their ability to effectively classify and predict the severity and outcome of COVID-19 [93]. These datasets enable the simultaneous quantification of multiple proteins from a single sample and measurement. Particularly in severe cases of COVID-19, proteomic predictors have shown superior performance compared to commonly used scoring systems such as acute physiology and chronic health evaluation (APACHE II), Charlson comorbidity index (CCI), and SOFA scores (mortality predictive value) [94]. Additionally, proteomics has significantly accelerated the characterization of the antiviral host response, leading to a deeper understanding of COVID-19. This advancement has been achieved by identifying the involvement of the complement cascade, coagulation system, and apoprotein function in the differences observed in COVID-19 pathology [95].

Nutritional Proteomics in Disease Treatment

The importance of nutrition as a lifestyle optimization in cancer prevention and treatment has been studied by many scientists. Different nutritional interventions have been investigated, such as calorie restriction, fasting practices, carbohydrate restriction, and their influence on cancer biology. Furthermore, the role of proteomics in identifying cancer biomarkers and comprehending the molecular impacts of nutrition through nutrigenomics was studied [57]. Nutrient restriction, including fasting, has a broad impact on overall health and development of diseases. It might influence the initiation, progression, and treatment of cancer. Researchers believe that incorporating fasting alongside standard treatments can improve the effectiveness of cancer treatment. The potential of nutrigenomics lies in its ability to uncover fasting molecular mechanisms and identify biomarkers for nutritional interventions in cancer treatment. This can be accomplished by conducting quantitative proteomic studies that involve fasting in tumorigenic cells and animal models. Researchers envision the future for nutritional omics as an analytic device to evaluate the metabolic state of tumors and determine the suitability of fasting as a treatment option for individual patients [57].

Over the past decade, proteomic technology and research have experienced significant progress, driven by advancements in high-throughput methods. These methods have facilitated the generation of vast and detailed datasets, while data mining techniques have aided in the identification of novel biomarkers crucial for early disease detection and treatment [95]. Lee *et al*. conducted a study to examine how a lack of vitamin K (VK) affects the proteins in the plasma of 500 Nepalese children aged 6-8 years. They measured the levels of lipids and a protein induced by VK absence-II (PIVKA-II). By using mass spectrometry, they identified proteins that are associated with VK status [94]. They showed that when there is a deficiency of VK (PIVKA-II >2 μg/L), it is connected to higher levels of low-density lipoproteins, total cholesterol, and triglycerides in the plasma. Among the 978 proteins that were observed in more than 10% of the children, five proteins were found to be associated with PIVKA-II levels, and seven proteins showed differences in abundance between children who were deficient in VK and those who had sufficient levels. Some of these proteins included coagulation factor-II, hemoglobin, and vascular endothelial

cadherin. Through analyzing the connections between proteins, the researchers discovered a strong positive relationship between the subunits of hemoglobin and certain enzymes that protect red blood cells from oxidative stress. This suggests possible links between coagulation, vascularization, and the impact of oxidative stress on red blood cells in relation to VK status. Their study emphasized the value of untargeted proteomics, which is a cutting-edge approach, in helping them understand the biological processes related to blood clotting, blood vessel formation, and the impact of oxidative stress on red blood cells associated with VK deficiency [95].

Proteomics has witnessed remarkable advancements, thanks to high-throughput methods, data mining, and the integration of artificial intelligence. These developments have led to the discovery of valuable biomarkers and opened doors to analyzing extensive clinical data. The future of proteomics holds the promise of a comprehensive understanding of single-cell biology and personalized medicine, fostering advancements in research and healthcare [96, 97].

Biomarkers Discovery

Biomarkers specific to a particular disease can be categorized into diagnostic, prognostic, and treatment-predictive biomarkers based on the info they deliver [97]. Diagnostic biomarkers are utilized to detect the presence of a disease or identify it at an early stage. Prognostic biomarkers are employed to predict the likelihood of disease recurrence, aggressiveness, and patient response to treatment with a particular drug [98]. Also, by employing proteomic techniques, researchers can identify biomarkers that help predict weight loss in individuals who are overweight or obese [99]. A frequently used biomarker in medicine is prostate-specific antigen (PSA). However, the detection of malignancies often occurs at advanced stages, leading to poor prognosis and limited treatment options. This is primarily due to the costly and time-consuming process of tracing biomarkers. It is crucial to develop a more efficient method for early detection, which requires a combination of different once-proteome data platforms [100]. As the expression of proteins changes during disease conditions within biological pathways, monitoring these altered proteins in tissue, blood, urine, or other biological samples can provide indications of the disease [99].

Recent studies have showcased the potential of proteomic profiling in forecasting weight loss, underscoring the significance of protein biomarkers in this context [101]. Moreover, proteomics plays a critical role in identifying drug targets through methods such as chemical proteomics and protein interaction networks [3]. Integrating proteomic profiling into personalized nutrition plans holds great promise for anticipating weight loss outcomes and enhancing overall health in individuals struggling with excess weight [101]. Once potential biomarkers are identified through the use of mass spectrometry, they should undergo thorough bioinformatics analysis and be validated across different groups of people to ensure their reliability [53].

Serum Biomarkers

Apart from proteomics, personalized nutrition plans for disease treatment have also been developed using other -omics approaches, such as genomics, transcriptomics, and metabolomics [102]. In a randomized dietary intervention trial involving 609 overweight/obese individuals, [101] analyzed 263 inflammatory and cardiovascular proteins before and after weight loss. They discovered that 102 proteins showed an association with baseline BMI levels. Additionally, in longitudinal analyses, they found that 130 proteins correlated with weight loss. Notably, the study revealed that baseline levels of Fibroblast Growth Factor 21 (FGF-21) had a significant predictive capacity for weight loss. Interestingly, there were no interactions observed between baseline protein levels and diet type regarding weight loss. These findings highlight the potential of investigating circulating proteins to gain insights into the underlying mechanisms of obesity, although their use in predicting weight loss outcomes and tailoring personalized dietary recommendations is limited [101].

By employing proteomics, scientists can gain valuable insights into the pathogenesis of Inflammatory bowel disease (IBD) and identify potential biomarkers for assessing disease activity, mucosal healing, and cancer progression [102].

When conducting biomarker discovery studies or assessing the clinical utility of biomarkers, it is important to take into account the variations in the sample matrix [103].

Meuwis and colleagues carried out a study in which they examined the blood samples of patients with inflammatory bowel disease (IBD), as well as healthy individuals and those with different types of inflammatory conditions. They used a technology called SELDI-TOF-MS to isolate and identify four proteins associated with acute-phase reactions, which could potentially be used as markers to indicate the activity of the disease. These proteins are platelet factor 4 (PF4), haptoglobin 2 (Hp2), fibrinogen alpha chain (FIBA), and myeloid-related protein 8 (MRP8) [104].

Serum protein biomarkers related to nutritional status could serve as interpreters of disease symptoms in COVID-19 patients before and following vaccination was examined. In pre-vaccine cohorts, proteomics analysis showed significant differences between groups. Serum proteins alpha-1-acid glycoproteins (AGPs) 1 and 2, C-reactive protein (CRP), and retinol-binding protein (RBP) increased with the severity of COVID-19 symptoms, while serum albumin, transthyretin (TTR), and serotransferrin (TF) decreased as symptomatology worsened [104].

The Implementation of personalized nutrition procedures, along with oral or enteral/parenteral supplements, can serve

to address protein and energy requirements in combating COVID-19 and to enhance the microbiota of the intestines and lungs [105]. By improving diet and incorporating formulations containing prebiotics or probiotics, these approaches can be joined to other interventions, such as vaccines, to effectively control COVID-19 [105]. Serum/plasma biomarkers offer valuable insights into dietary exposure and the impact of infectious and non-infectious diseases on nutritional metabolism [106].

Urine Biomarkers

Urine, a less intricate sample than plasma with more than 1500 proteins [107]. Additionally, urine demonstrates relatively stable protein composition and fragmentation, setting it apart from other biofluids like plasma or serum that can experience proteolytic degradation during and after sampling [107].

Proteomics is a promising path for investigating protein research. Different proteomics methods, including 2-dimensional difference gel electrophoresis (2D-DIGE), MALDI-TOF/MS, LC-MS/MS, and others, were performed to analyze patient serum and urine [108].

A powerful biomarker called neutrophil gelatinase-associated lipocalin (NGAL) and matrix metalloproteinase (MMP-9) was identified in the urine of breast cancer patients using a technique called gelatin zymography [109]. Also, matrix metalloproteinase (MMP-9) and ADAM 12 can be strong indicators of breast cancer when tested through zymography and immunoblotting with the help of ADAM 12 antibodies [110].

Researchers have identified certain biomarkers found in urine, such as stratifin, membrane metalloendopeptidase, Parkinson's protein 7, and tissue inhibitor of metalloproteinase 1, as dependable indicators of prostate cancer. This breakthrough was achieved through a range of methods, including LC-MS/MS, Western blot analysis, and quantification using selected reaction monitoring-MS [43]. Similarly, Li *et al*. [66] employed LC-MS/MS to confirm the suitability of osteopontin (SPP1), prothrombin (F2), pyridinoline, and deoxypyridinoline as prostate cancer indicators in their 2015 study. Quantitative iTRAQ, LC-MS/MS, and immunoblotting on urine samples were carried out, uncovering beta-2-microglobulin (B2-M), Prostate cancer Gene 3 (PGA3), and Mucin 3 (MUC3) as dependable prostate cancer markers. Additionally, through the utilization of 2D-DIGE-MS and immunoturbidimetry, determined that transferrin, alpha-1-microglobulin, and haptoglobin had the potential to serve as urinary indicators for prostate cancer [111].

Apolipoprotein D, insulin-like growth factor-binding protein 3, and ApoD levels were significantly elevated in Alzheimer’s disease patients in comparison to the control group, as determined through enzyme-linked immunosorbent assays [112]. Also, another biomarker that is found to be raised in the urine of patients suffering from diabetic nephropathy is the α1-antitrypsin. The techniques used to analyze it were the 2D-DIGE and ELISA [113]. In a different investigation, Pejcic *et al*. identified ubiquitin ribosomal fusion protein (UbA52) as a valid biomarker using the SELDI technique [112]. Additionally, Dihazi *et al*. employed SELDI and discovered the selective absence of the processed form of ubiquitin in the urine of patients [113, 114].

A promising biomarker for renal fibrosis is, the WNT1-inducible signaling pathway protein-1 [115].

Pharmacogenomics Integration

Proteins offer an ever-changing view of how cells respond to drug treatments. For precision medicine to evolve, it's pivotal to connect genetic studies with in-depth analyses of the proteome. The essence of precision medicine should encompass both pharmacogenomics and the emerging realm of pharmacoproteomics, which taps into proteomic technologies to delve into drug discovery [116]. In the broader context of 'omics' strategies, integrating transcriptomics is essential due to the potential differences that can arise between mRNA and protein expressions [117]. Customized approaches in the field of 'omics,' involving both the genetic and protein levels, are actively enhancing our grasp of disease mechanisms and how medications work. These approaches allow us to uncover, identify, and closely track new biomarkers for a wide range of complex diseases and their treatments. By combining information from pharmacoproteomic profiles with pharmacogenomics databases, precision medicine could eventually become a reality, tailoring the most suitable treatment plan for each individual through diagnostic tests. It's clear that findings from various 'omics' areas such as pharmacogenomics, transcriptomics, pharmacoproteomics, as well as related fields such as toxicoproteomics and pharmacometabolomic, shouldn't be considered in isolation but rather should work together to provide comprehensive insights [118].

Future Directions in Proteomics Research

Understanding how our bodies react to nutrition-based treatments has grown increasingly over the years. This is where nutrigenetics and nutrigenomics, along with technologies like omics, come in [119]. The joined use of metabolomics, proteomics, and genetics, along with anthropometry and clinical biomarkers, will provide indicators for fundamental health mechanisms [38]. Nutritional proteomics is a rapidly developing field and many exciting discoveries are being made every day [120].

Recent research discussed the future of nutritional proteomics, the future of the use of mass spectrometry-based proteomics, and next-generation protein sequencing technologies that may shape the future of proteomics [121]. The potential of proteomics as a biomarker in food authentication, quality, and safety was also discussed by Afzaal *et al*. The research highlighted the wide-ranging applications of proteomics in food-related fields [7].

By 2035, it is predicted that options like plant-based, microorganism-derived, and animal cell-based alternatives to animal-based products such as meat, fish, eggs, and dairy could comprise around 11% of the world's protein consumption. And if there's strong backing from regulators and significant leaps in technology, these alternatives might even grow to represent a remarkable 22% of the total protein intake. Furthermore, the transition towards plant-based meat and eggs alone may have a significant impact. It might lead to carbon emissions reduction equivalent to what Japan emits in a whole year, save a water amount that could supply London for four decades, and contribute positively to preserving biodiversity and ensuring food security. According to a recent report by Blue Horizon and Boston Consulting Group, the alternative protein market, valued at $290 billion, forms the cornerstone of a more ecologically balanced food system.

Conclusion

In conclusion, the field of nutritional proteomics holds great promise in unraveling the intricate relationship between diet, proteins, and human health. By studying the effects of nutrition at the molecular level, we gain insights into the mechanisms underlying disease prevention, early detection, and personalized treatment. Through advances in technology and integrative approaches with other omics disciplines, nutritional proteomics offers a pathway to tailor interventions that optimize individual well-being. As we move forward, continued research and collaboration are key to unlocking the full potential of this field, shaping a future where personalized nutrition becomes a cornerstone of healthcare strategies.

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