

Original Research

Received 15 March 2026

Revised 20 April 2026

Accepted 08 May 2026

Natural Resources for Human Health 2026, Vol. 6 (3): 310–318

KEYWORDS:

Functional foods; Artificial intelligence; Systems biology; Multi-omics; Machine learning; Network pharmacology; Molecular mechanisms; Bioactive compounds; Precision nutrition; Gut microbiome.

Molecular Mechanisms of Functional Foods Revealed by Artificial Intelligence and Systems Biology

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ABSTRACT: Based on their various bioactive compounds, including polyphenol, flavonoids, carotenoids, dietary fibres, probiotics, and omega-3 fatty acids, functional foods have proven to be an effective way to promote health and to reduce the risk of chronic diseases. Numerous studies have shown their beneficial effects, but the complexity of the molecular mechanisms responsible for such activities continues to be poorly understood because of the intricacies of gene/protein/metabolite/signaling pathway/gut microbiome interactions. In recent years, the use of artificial intelligence (AI) and systems biology has revolutionized functional food research by facilitating the systematic analysis of complex multidimensional biological information and by helping identify molecular targets, the molecular signatures of the disease under investigation, and regulatory networks. The advancement of machine learning, deep learning, network pharmacology, molecular docking, and multi-omics integration has sped up the identification of bioactive molecules, the prediction of food–target interactions, the pathway enrichment analysis, and the interpretation of the mechanisms underlying the biological responses. These computational tools can also contribute to precision nutrition, by combining individual genomic, metabolomic, and microbiome data to create tailored nutrition plans. However, data quality, model interpretation and understanding,

standardization of multi-omics data, clinical validation, and regulatory acceptance remain obstacles to wider translation into healthcare practice. The review aims to summarise the molecular mechanisms that underlie the biological effects of functional foods and to emphasise the emerging contributions of AI and systems biology to understanding these mechanisms. In addition, this work addresses challenges and opportunities at the intersection of computational intelligence and nutrition and highlights new technologies and future opportunities in this field to facilitate the discovery of functional foods and the field of precision nutrition. The synergy of AI, systems biology and functional food research will create a strong foundation for evidence-based dietary interventions and future generation preventive health.

1. INTRODUCTION

The concept of functional foods has been attracting a lot of interest as a part of preventive health care because they offer physiological benefits other than nutrition. Conventional foods are those that provide essential nutrients and functional foods have biologically active components that can modulate molecular and cellular mechanisms involved in health maintenance and disease prevention. Naturally occurring bioactive compounds such as polyphenols, flavonoids, carotenoids, glucosinolates, dietary fibers, probiotics, prebiotics and omega-3 fatty acids have shown different biological activities that have been associated with lower risk of cardiovascular diseases, metabolic disorders, neurodegenerative disorders, cancer, chronic inflammation and immune dysfunction (1,2). The rising concern among consumers for nutrition-based disease prevention and the spread of chronic non-communicable diseases have also boosted efforts to identify and mechanistically study the functional food components. Although there is a significant amount of experimental evidence, proving the health promoting properties of functional foods, the exact molecular mechanisms are still difficult to be determined. Most of the functional food constituents have pleiotropic activities, which means they can simultaneously interact with many molecular targets, signaling pathways, metabolic networks and microbial community (3). The intricate interactions include the synergistic control of the oxidative stress response, inflammatory mediators, cellular metabolism, apoptosis, autophagy, mitochondrial function, and immune signaling. Moreover, there is substantial inter-individual variation in response to the intervention of functional food components which is related to genetic background, age, diet, gut microbiota composition, environmental exposure and lifestyle, a factor that complicates mechanistic interpretations even more (4). While essential for confirming biological activity, conventional experimental methods tend to be labor intensive, time consuming and lack the capacity to capture the dynamics of interactions taking place across several biological systems. With the development of high throughput technologies such as genomics, transcriptomics, proteomics, metabolomics, lipidomics and microbiome profiling, there is growing amounts of biological data describing effects on functional foods at different molecular levels (5). But in order to offer these diverse data sets in a coherent and biological sense, sophisticated computational methods are needed that can find hidden relationships, make predictions about molecular interactions, and enable the building of comprehensive biological networks. The fields of Artificial Intelligence (AI) and Systems Biology have become transformative tools that are combining computation and experimentation to solve these problems. Machine learning and deep learning algorithms are capable of analysing complex multidimensional data sets which can help in the discovery of biomarkers, prediction of food–target interactions, disease classification, and personalised nutritional recommendations. At the same time, systems biology offers a more comprehensive way to analyze the interaction and interdependence of genes, proteins, metabolites, signaling pathways and the gut microbiome as interconnected networks of organisms. Network pharmacology, molecular docking, pathway enrichment analysis, protein–protein interaction mapping and multi-omics integration have significantly enhanced the understanding of functional food bioactivity mechanism and sped up new drug target discovery (6). In this review, the molecular mechanisms by which functional food bioactive compounds affect human health are reviewed, critically, and the use of artificial intelligence and systems biology is discussed as it is revolutionizing mechanistic investigation in nutritional science. Special focus is given to AI-driven multi-omics integration, computational predictions of molecular targets, network-based pathway analyses, and novel precision nutrition approaches, offering novel prospects for evidence-based functional food studies and future clinical applications.

2. MOLECULAR MECHANISMS OF FUNCTIONAL FOODS AND BIOACTIVE COMPOUNDS

Functional foods offer benefits that are from different bioactive components that act through various molecular targets and pathways, and not one single mechanism. Unlike traditional pharmacological drugs, which usually act on a single target molecule, compounds from functional foods have pleiotropic effects and multiple actions that cover oxidative stress, inflammatory response, cellular metabolism, immune function, mitochondrial activity, apoptosis, autophagy and gut microflora. This multi-target mode of action allows the functional food to affect the pathogenesis of many chronic diseases such as cardiovascular disease, type 2 diabetes mellitus, obesity, neurodegenerative disorders, inflammatory bowel disease and several types of cancer (7). Elucidation of such interrelated molecular mechanisms is essential for setting evidence-based dietary guidelines and for finding new nutritional interventions for disease prevention. Polyphenols are one of the most widely studied classes of functional food bioactives, due to their strong antioxidant and anti-inflammatory effects. Polyphenols are found in abundance in fruits, vegetables, tea, cocoa, berries and whole grains, and they neutralize the reactive oxygen species while also stimulating the body's own antioxidant defense mechanisms. These antioxidants do not just act directly on antioxidants, but they control intracellular signaling pathways that facilitate redox homeostasis. A key mechanism is activation of nuclear factor erythroid 2-related factor 2 (Nrf2) which upregulates antioxidant enzymes, such as heme oxygenase-1, superoxide dismutase, catalase, glutathione peroxidase, and NAD(P)H quinone oxidoreductase-1. The activation of the pathway of Nrf2 increases the resistance of cells to oxidative stress and reduces oxidative damage caused by ageing and the progression of chronic diseases (8). Concurrently, many functional food bioactives are known to reduce chronic inflammation by inhibiting the nuclear factor-kappa B (NF- κ B) signaling pathway. The sustained NF- κ B activation leads to increased pro-inflammatory cytokines, chemokines, cyclooxygenase-2, inducible nitric oxide synthase and adhesion molecules, all of which participate in chronic inflammatory diseases. The anti-inflammatory effects of polyphenols on NF- κ B activation have been consistently demonstrated, leading to decreased production of tumor necrosis factor- α , interleukin-1 β , and interleukin-6 among other inflammatory mediators. These compounds have the ability to block the molecular feedback loop responsible for chronic inflammation and tissue damage, while simultaneously reducing oxidative stress and inflammatory signaling (9). In addition to its antioxidant and anti-inflammatory properties, functional food ingredients exert effects on cell metabolism via various pathways of nutrient sensing. The AMPK pathway is a crucial metabolic pathway responsible for the regulation of energy homeostasis by promoting glucose uptake, boosting fatty acid oxidation, inhibiting lipid biosynthesis, and increasing insulin sensitivity. The bioactive components in tea, such as catechins, anthocyanins, berberine and omega-3 fatty acids, can activate AMPK, which helps to regulate metabolism and lowers the risk of obesity, metabolic syndrome and type 2 diabetes. In addition, modulation of phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) and mammalian target of rapamycin (mTOR) signaling has been shown to affect cell survival, protein synthesis, autophagy and cellular proliferation, providing a broad metabolic effect of dietary bioactives (10). Interactions between functional foods and gut microbiota are another crucial mechanism that has emerged as a key contributor to host metabolism and immune regulation. Dietary fibers, prebiotics, probiotics and polyphenols have the effect of altering the microbial composition by positively influencing the bacteria that are beneficial and reducing the pathogenic bacteria in the body. Short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate are produced by microbial fermentation of dietary substrates, and these compounds have a protective effect on the integrity of the intestinal barrier, on the differentiation of immune cells, on glucose metabolism and on reducing systemic inflammation. The metabolites produced by these microbiota also modulate host gene expression via epigenetic control and other pathways that extend beyond the gastrointestinal tract, reflecting the intricate interactions between food, microbes, and host physiology (11). Together these interrelated molecular pathways provide evidence that bioactive compounds in functional foods modulate human health beyond the individual (but integrated) effects of oxidative stress, inflammation, metabolic signaling and gut microbial homeostasis. The relationships of these pathways are summarized in Figure 1.

Another important pathway that is regulated by functionality food bioactive compounds is the so called Mitogen-activated protein kinase (MAPK) pathway. The MAPK family of kinases, such as extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 MAPK, regulate cellular proliferation and differentiation, apoptosis, inflammation, and stress responses. Many dietary phytochemicals regulate MAPK signaling in a context-dependent fashion, attenuating overactive inflammatory activation, while maintaining normal cell functions. Curcumin, sulforaphane, lycopene, genistein and catechins have been shown to be able to modulate the MAPK-mediated transcriptional response, which helps to decrease oxidative damage and inflammatory cytokine production. In addition, simultaneous modulation of MAPK and NF- κ B signaling further enhances anti-inflammatory and cytoprotective properties of functional foods, illustrating the interlinked nature of intracellular

signaling pathways and networks, not just individual signaling molecules (12). Apart from its role in signaling pathways, functional food components also modulate apoptosis and autophagy, thus affecting cellular homeostasis. Apoptosis is essential for the elimination of damaged and/or dysfunctional cells, while autophagy is important for the removal of intracellular defective organelles and protein aggregates to maintain cellular quality control.

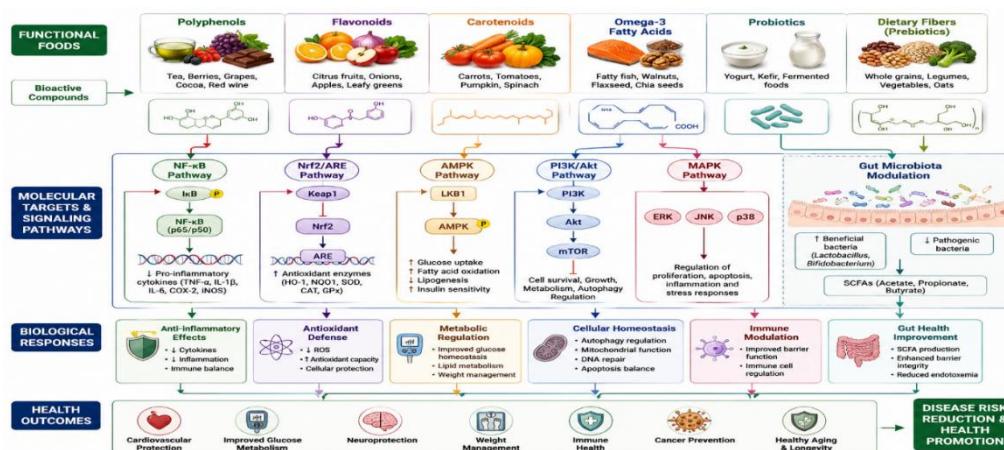


Figure 1. Molecular mechanisms underlying the health-promoting effects of functional food bioactive compounds

The imbalance in either process plays a role in cancer, neurodegenerative diseases, metabolic diseases and premature aging. A number of naturally-occurring bioactive molecules have been identified to restore the balance between apoptosis and autophagy through the modulation of Bcl-2 family proteins, caspases, Beclin-1, LC3, and mTOR-dependent signaling. In physiological conditions, these mechanisms help to maintain the integrity of mitochondria, limit oxidative damage, and ensure cell survival, whilst in abnormal or malignant cells selectively inducing their death, thus showing context-specific effects of functional food bioactives (13). New evidence also shows that there is a biological activity of bioactive compounds in food that can be explained by epigenetic regulation. Polyphenols, isothiocyanates and other phytochemicals regulate DNA methylation, histone modification and the expression of microRNA, which affects the transcription of genes without altering the DNA sequence. This epigenetic regulation helps to regulate inflammation, antioxidant response, lipid metabolism, glucose maintenance, and immune function over the long term. In addition, there is a complex interaction between diet, gut microbiota, and epigenetic mechanisms, which forms an integrative regulatory network that is connected with nutrition exposure, gene expression and disease susceptibility. The observation also gives a molecular basis for the long-term health promotion effect of functional foods and substantiates the disease prevention effect of functional foods in different populations (14). The diversity of the biological functions shown by the functional foods is caused by the diversity of functional molecules that are present in these foods and the complexity of their molecular targets. Single foods may exhibit several classes of bioactive compounds with multiple signaling processes, resulting in additive and/or synergistic physiological effects. Thus, assessment of functional foods should be done from a system perspective, as opposed to reductionist approaches involving individual compounds or single targets. There is a vast molecular diversity in the functional foods that are consumed worldwide and their bioactive compounds, which target various molecular pathways in the body, with the associated health benefits summarized in Table 1, representative examples are included (15).

Table 1. Bioactive Functional Foods: Molecular Targets, Biological Activities, and Clinical Applications.

Functional Food	Major Compound(s)	Bioactive	Major Molecular Target(s)	Primary Effect(s)	Biological	Therapeutic Potential
Green tea	Epigallocatechin-3-gallate Catechins	(EGCG),	Nrf2, NF- κ B, AMPK	Antioxidant, anti-inflammatory, metabolic regulation	anti-	Cardiovascular disease, obesity, cancer prevention

Turmeric	Curcumin	NF- κ B, MAPK, PI3K/Akt, mTOR	Anti-inflammatory, antioxidant, apoptosis regulation	Cancer, arthritis, inflammatory disorders
Blueberries	Anthocyanins	AMPK, Nrf2	Antioxidant, glucose homeostasis	Diabetes, cognitive decline
Tomatoes	Lycopene	MAPK, PI3K/Akt, Nrf2	Oxidative stress reduction, anti-proliferative activity	Cardiovascular disease, prostate cancer
Citrus fruits	Hesperidin, Naringenin	NF- κ B, PI3K/Akt	Anti-inflammatory, endothelial protection	Hypertension, metabolic syndrome
Cruciferous vegetables (Broccoli)	Sulforaphane	Nrf2, MAPK	Detoxification, antioxidant defense	Cancer chemoprevention
Fatty fish	EPA, DHA (Omega-3 fatty acids)	PPARs, AMPK, NF- κ B	Lipid metabolism, inflammation suppression	Cardiovascular disease, neurodegenerative disorders
Yogurt and Fermented Foods	<i>Lactobacillus</i> , <i>Bifidobacterium</i> spp.	Gut microbiota, TLRs, NF- κ B	Immune modulation, intestinal barrier integrity	Gastrointestinal disorders, immune health
Oats	β -Glucan	Gut microbiota, AMPK	Cholesterol reduction, glycemic control	Diabetes, hypercholesterolemia
Garlic	Allicin, Organosulfur compounds	NF- κ B, Nrf2	Antioxidant, antimicrobial, anti-inflammatory	Cardiovascular disease, infectious diseases

3. ARTIFICIAL INTELLIGENCE AND SYSTEMS BIOLOGY IN FUNCTIONAL FOOD RESEARCH

Conventional reductionist research on functional food compounds or isolated molecular targets has been constrained by the growing complexity of functional food research. Functional foods contain hundreds of chemically diverse bioactive compounds that can interact simultaneously with hundreds of genes, proteins, metabolites, signaling pathways and microbial communities. These multidimensional interactions create large amounts of biological data that can't be easily analyzed with a conventional approach. Therefore, the fields of artificial intelligence (AI) and systems biology have become complementary computational areas that can combine disparate pieces of biological information into a whole-system mechanistic model. They can be used in combination to reveal unknown molecular interactions, to predict biological effects, to reveal molecular markers, and to elucidate the complex mechanisms that underlie the effect of functional foods on human health (16). AI is a wide range of computational methods that can identify patterns, learn from vast amounts of data and create predictive models with limited human interaction. Various machine learning algorithms (random forests, support vector machines, gradient boosting methods, artificial neural networks) are now useful in predicting the biological activity of food derived bioactive compounds. The algorithms are able to process very large quantities of chemical, biological and clinical data and construct correlations between molecular structure and biological function, which is the key to discovering new functional ingredients more rapidly. In metabolomics, transcriptomics, and food image analysis, similar results can be obtained using deep learning which can learn complex nonlinear features from high-dimensional data. The development and proliferation of multi-omics technologies have greatly improved the AI-based functional food research. Genomics offers data on genetic variation that affects the metabolism of nutrients, while transcriptomics offers data on gene expression that are the result of dietary interventions. Proteomics will identify differences in protein abundance and protein post-translational modifications, and metabolomics will identify metabolites that are directly linked to the physiological responses to the use of functional food. At the same time, microbiome sequencing has uncovered the complex interactions between the food components and gut microbial communities. These

multi-omics data are used to build predictive models using AI algorithms that can discover molecular biomarkers, biological pathways, and individual dietary responses that would be hard to identify using traditional statistical methods (18). Systems biology complements AI by offering a comprehensive approach to analyze biological systems as complex networks of molecules instead of as individual parts. Systems biology uses a combination of genomic, proteomic, metabolomic and microbiome information to provide a system-wide view of how cell metabolism responds to dietary bioactive compounds rather than just single genes or proteins. Network-based analyses can be used to visualize interactions between genes, proteins, metabolites and signaling molecules and identify important regulatory hubs that mediate physiological effects. These strategies have contributed greatly to the understanding of the overall effect of multiple components of a functional food on inflammation, oxidative stress, immune-modulation, cellular metabolic pathways and disease progression, where the effects of two or more food components are often interconnected and mediated synergistically. The network pharmacology is one of the most influential systems biology approaches, which has attracted much attention due to its capacity of multi-component and multi-target interactions. Network pharmacology is a paradigm which recognizes that dietary bioactive compounds may have therapeutic effects by regulating multiple molecular pathways, in contrast to the classical pharmaceutical model treating one drug at one target. The combination of AI and network pharmacology allows for automated prediction of compound–target interactions, building protein–protein interaction networks, pathway enrichment analyses and identification of key nodes in the signaling pathways linked to disease prevention. These computational approaches have led to a marked speedup of mechanistic studies and have lessened the experimental costs and increased the efficiency of the discovery of functional food ingredients (20).

The molecular docking and molecular dynamics simulation methods are essential computational tools for the validation of the interactions predicted by the AI models between functional food bioactive compounds and their molecular targets. Molecular docking can predict the binding affinity and interaction pattern of phytochemicals with target proteins, and molecular dynamics simulations can be used to assess the stability and conformational changes of the phytochemical-protein complex under physiological conditions. Combined with these computational methods, the use of AI allows for a virtual screening of thousands of natural compounds, prioritization of potentially promising compounds, and prediction of their therapeutic properties, before even conducting experiments. This strategy significantly decreases research costs and allows bioactive molecules to be identified that can affect signaling pathways in inflammation, oxidative stress, metabolic disorders, and cancer (21). One of the biggest drawbacks of traditional machine learning models is their lack of interpretability, which has been tackled by recent breakthroughs in explainable artificial intelligence (XAI). Even very accurate predictive models are useful, but so is knowing the reason behind the computations. XAI algorithms highlight specific molecular characteristics, biomarkers, or biological processes that make the greatest impact on the model's predictions, enhancing transparency and trust in AI-driven nutrition research. This interpretability makes it easier to validate computational results by experimental scientists and easier to accept the use of AI in decision-making for functional food product development (22). AI, systems biology, and precision nutrition are revolutionizing the design of personalized nutrition interventions. As individual responses to functional foods can greatly differ based on their genetic makeup, metabolic phenotype, lifestyle, age, and gut microbiota composition, the potential risks and benefits of consumption should be assessed on a case-by-case basis. The AI algorithms combine genomic, transcriptomic, metabolomic, microbiome and clinical data to determine patterns of eating that bring the greatest health benefits to certain patients or patient groups. New ideas like digital twins, virtual computational models of individual physiological systems, will also allow for simulation of nutritional intervention prior to application, which will further aid in the development of personalized disease prevention and optimized dietary recommendations (23). In sum, AI and systems biology have laid the foundation for a comprehensive computational framework for the characterization of molecular mechanisms of functional foods. The multi-omics integration, machine learning analysis, network pharmacology, molecular docking, protein–protein interaction, pathway enrichment, and biomarker discovery enable a comprehensive understanding of the intricate relationship between dietary bioactive compounds and biological systems like never before. Overall computational workflow for mechanistic study of functional food is presented in Figure 2.

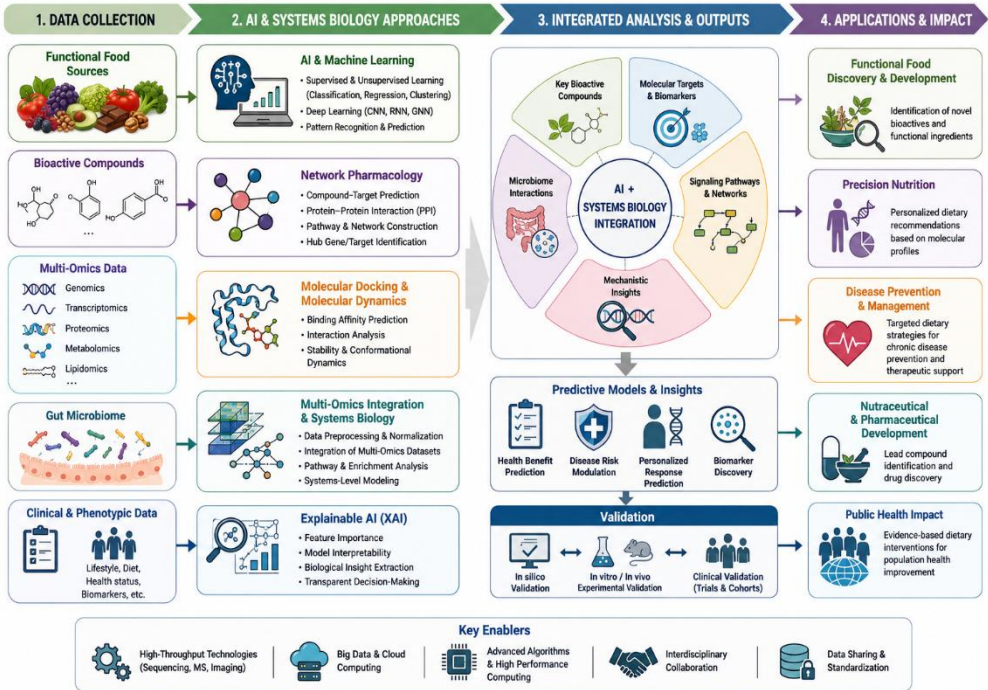


Figure 2. Artificial intelligence and systems biology workflow for elucidating the molecular mechanisms of functional foods

There are differences in the analytical capabilities and requirements in terms of computational load of current AI algorithms and systems biology platforms and the applications of these in functional food research. Some algorithms work best for predictive modelling and biomarker discovery, others for network reconstruction, pathway analysis or prediction of molecular interactions or integration of multi-omics data. Knowledge of the pros and cons of these computational methods is crucial to ensure the selection of the right analytical methods, and to make the biological interpretation more reliable. The available principal AI algorithms and systems biology tools which are currently used in functional food research are presented in Table 2 (24).

Table 2. Artificial intelligence algorithms and systems biology tools used in functional food research

Tool	Primary Application	Key Advantage
Machine Learning	Bioactivity prediction	High predictive accuracy
Deep Learning	Multi-omics analysis	Identifies complex patterns
Network Pharmacology	Compound–target interaction analysis	Multi-target mechanism prediction
Molecular Docking	Protein–ligand interaction	Rapid target validation
Multi-omics Integration	Biomarker and pathway discovery	Systems-level understanding
Protein–Protein Interaction (PPI) Analysis	Network reconstruction	Identifies hub genes/proteins
Explainable AI (XAI)	Model interpretation	Improves transparency

4. CHALLENGES AND FUTURE PERSPECTIVES

Although great strides have been made in the field of artificial intelligence (AI) and systems biology, there remain some scientific and technical obstacles to their broader use in functional food research. Multi-omics data from genomics, transcriptomics, proteomics, metabolomics, and microbiomes is highly heterogeneous and a primary barrier. However, the differences in methods, sample preparation, analytical platforms, and data preprocessing can diminish the reproducibility and make it difficult

to compare data from different studies. Lack of uniform data formats and well-curated and publicly available high-quality databases also hinder the creation of comprehensive AI models with the potential to generalize to different populations and dietary interventions (25). Another significant drawback is the lack of interpretability of AI algorithms. Deep learning models are highly predictive, but often are "black-box" models, where it is hard to understand the biology behind prediction. The lack of transparency makes researchers, clinicians and regulators less confident. Explainable Artificial Intelligence (XAI) provides some hope to address this challenge by locating the molecular characteristics and biological pathways that underlie model predictions and enhance interpretability and support experimental validation (26). There is still another challenge to be solved: clinical translation. In many cases computational predictions are based on in vitro experiments, animal models or retrospective data sets, and need to be carefully validated with well-designed human clinical studies. It is important to note that since there are many differences in responses to functional foods—due to genetic differences, age, lifestyle, diet, gut microbiota composition, and exposure to their environment—a one-size-fits-all approach to dietary recommendations is not appropriate (27). Further studies need to leverage AI and the latest systems biology tools, such as single-cell omics, spatial transcriptomics, digital twins, and real-time health monitoring via wearable devices. These technologies could help to develop dynamic models of physiology at the level of individual people, which could be used to predict individual reactions to functional foods more accurately. The addition of electronic health records, ongoing metabolic monitoring, and microbiome profiling will further enhance evidence-based precision nutrition strategies (28). Implementation of these new technologies will need interdisciplinary efforts from nutrition scientists, computational biologists, clinicians, bioinformaticians, data scientists, and regulatory authorities. Creating common analytical pipelines, enhancing data sharing and creating clear regulatory systems are going to be critical to bring computational discoveries into the realm of clinically relevant nutritional interventions. AI-based systems biology will advance functional food discovery, mechanistic understanding, and personal nutrition planning for disease prevention and health improvement with ongoing technological advancements and validation (29,30).

5. CONCLUSION

The potential of functional foods as components of preventive medicine is due to their diverse bioactive compounds that can modulate several molecular pathways related to oxidative stress, inflammation, metabolism, immune regulation and gut microbiota homeostasis. Mechanistic investigation has undergone a paradigm shift in recent years, with the advent of artificial intelligence and systems biology, which has allowed multi-omics data to be integrated, molecular targets to be predicted, biological networks to be reconstructed, and clinically relevant biomarkers to be identified. Machine learning, deep learning, network pharmacology, molecular docking, and multi-omics integration are some computational tools that offer a holistic approach to decipher complex interactions between dietary bioactives and human biological systems. However, there are ongoing issues of clinical validation, standardization and interpretability of models, and data quality that dampen the potential for widespread adoption. Overcoming these limitations with the help of explainable AI, standardized analytical pipelines and interdisciplinary collaboration will be essential for turning these computational findings into actionable nutrition interventions. The future of functional food research will see further advancements with the integration of systems biology and AI, as this new combination holds the potential to revolutionize precision nutrition, personalize food recommendations, and inform evidence-based dietary strategies for disease prevention. Overall, these advances can pave the way toward the connection of nutritional science to precision healthcare, which will help enhance population health and help properly manage chronic diseases with scientifically proven functional food interventions.

DECLARATIONS

Funding: The authors received no specific financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Author Contributions: All authors contributed substantially to the conception, literature review, manuscript preparation, critical revision, and approval of the final version of the manuscript.

Ethical Approval: Ethical approval was not required because this study is a review article based exclusively on published literature.

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