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Biomedicine REVIEW

Advancements in precision nutrition: Targeted strategies for personalized health

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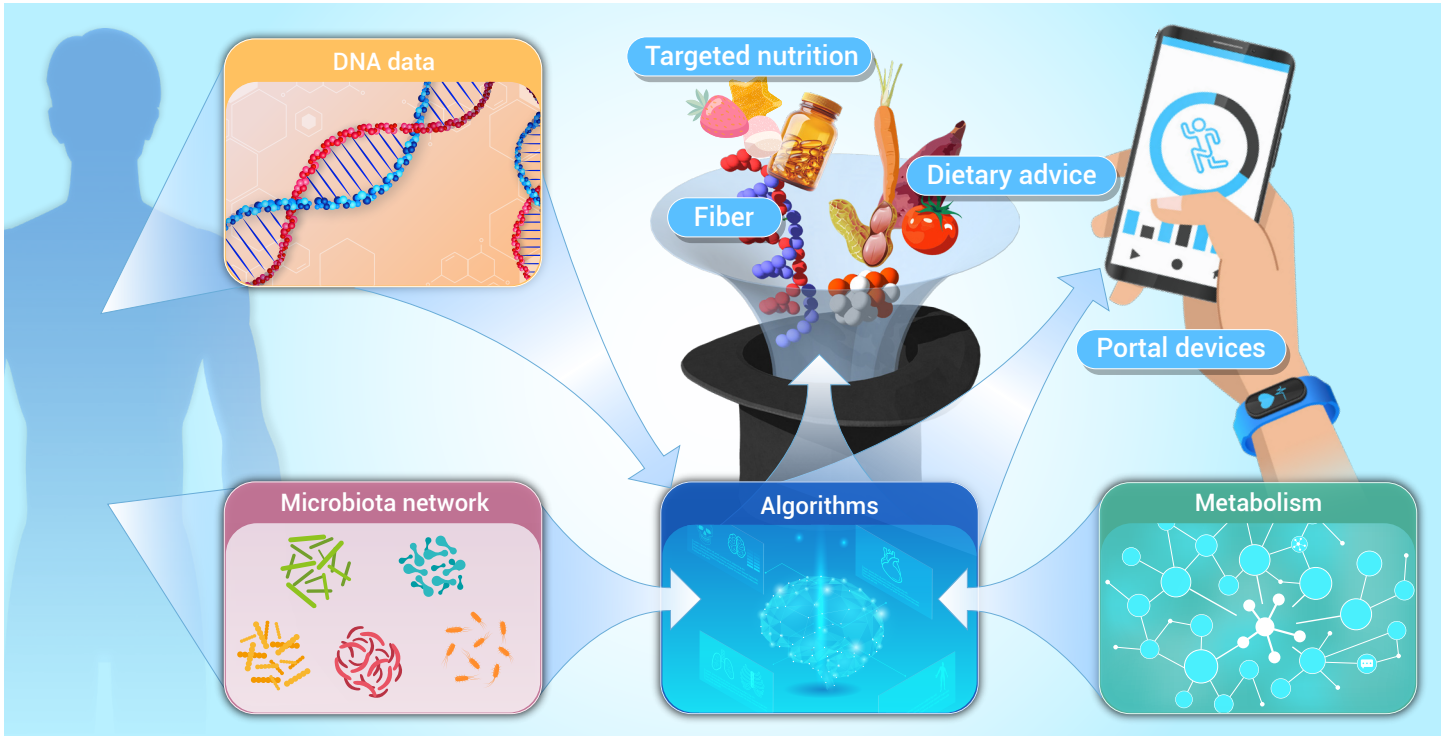
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Individual biological differences and health status advocate precision nutrition.
- Wearable sensors and portable devices gain instant individual-specific data.
- Artificial intelligence helps to collect, handle, and evaluate abundant information.
- Targeted nutrition is a favorable approach for developing precision nutrition.

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As the need for more effective nutritional interventions grows, precision nutrition has emerged as a strategy that leverages individual characteristics such as health status, genetic makeup, epigenetic profiles, and microbiota profiles to develop personalized nutrition plans tailored to treat and prevent disease. This strategy involves identifying an individual's health status through specific biomarkers, collecting personalized data via portable testing devices or digital tools, and managing individual-specific information via various algorithms. This review highlights advances in the biological underpinnings of precision nutrition, including understanding interindividual variation, designing target-specific nutrition plans, and addressing the challenges and opportunities of precision nutrition. Furthermore, targeted nutrition which focuses on delivering and releasing specific nutrients to particular sites in the body was explored as a recent innovation within precision nutrition. This review primarily examines targeted nutrition involving the controlled delivery of proteins/peptides, probiotics, fatty acids, polyphenols, and carotenoids, with a focus on the treatment of diseases affecting specific organs.

INTRODUCTION

Precision nutrition, or personalized nutrition, encompasses the development of tailored strategies for each person by taking into account a comprehensive range of factors, including genetics, epigenetics, microbiota, health status, location, environment, and lifestyle.[1,2] This approach aims to acknowledge individual information and guide dietary practices in a profound manner to prevent disease and promote health through effective nutritional interventions. For precision nutrition, there is a strong emphasis on carefully selecting appropriate food components within one's daily diet. From a dietary standpoint, precision nutrition plays a vital role in the prevention of chronic diseases in individuals.

In the fourth century B.C., Hippocrates highlighted the importance of balanced nutrition in maintaining good health and recognized the potential of food as a form of medicine.[3] It was not until the chemical-analytical era, which emerged in the late 19th century, that people began to understand the specific compositions of food and develop methods for identifying "nutrients", including macronutrients (such as proteins, fats, and carbohydrates) and micronutrients (such as vitamins and minerals).[4] In contrast, the biological era has provided insights into the body's metabolic pathways, and advancements in technology have propelled human nutrition into the realm of molecular nutrition.[5] A major milestone in the pursuit of precision nutrition occurred in 2000 with the completion of the human genome sequence map, which laid the foundation for incorporating genetic information into the understanding of precision nutrition.[6] Another noteworthy breakthrough was the development of a machine learning algorithm capable of predicting glycemic response. This algorithm integrates various factors, such as anthropometrics, physical activity, dietary habits, blood parameters, and the gut microbiota.[7] More recently, the advent of genetic tests, advanced computational data-driven technologies, and "omics" tools has provided extensive opportunities for realizing precision nutrition.[8] In Japan, initiatives such as Health Care 2035 and Society 5.0 have encouraged individuals to actively participate in health management by preventing disease, standardizing care, and effectively managing digital technology and personal data.[9] As human society continues to evolve and technology progresses, precision nutrition has garnered significant attention on a global scale.

Dietary intake is challenging to characterize clearly due to the intrinsic complexity of food. Beyond essential nutrients and health-promoting components, such as carbohydrates, lipids, proteins, vitamins, minerals, dietary fiber, and polyphenols, food also contains non-nutritive constituents like food additives. Since food exhibits emergent properties beyond the sum of its parts, variation in structure and composition lead to distinct behaviors in absorption, digestion kinetics, and metabolic and physiological responses.[10] For instance, the fat component in cocoa liquor protects cocoa polyphenols through micellization within liposomes, thereby enhancing cocoa polyphenols' stability during digestion. Polysaccharides and fiber can change protein digestion kinetics. The decreased proteolysis may result from electrostatic interactions between peptides, proteins and polysaccharides restricting access to the enzyme cleavage site.[11] Besides, phytic acid is a common inhibitor of mineral absorption. It binds zinc more strongly than iron, thus inhibiting zinc uptake more effectively than that of iron.[12] Moreover, foods exhibit variable biological properties, including growth stimulation and immune modulation.[13-15] Imbalances in nutritional status can contribute to the development of human diseases.[16] Therefore, precision nutrition holds promise for preventing or reversing conditions such as obesity, diabetes, cardiovascular diseases, chronic diseases, and metabolic syndromes.[17] It is crucial to identify approaches that provide appropriate nutritional content in the right proportions at the optimal timing and that are tailored to individual needs, similar to the concept of selecting appropriate medications for specific patients.[18] In essence, it is imperative to integrate individual characteristics with the properties of food to achieve successful precision nutrition interventions.

Precision nutrition necessitates accurate assessment and precise measurement of the molecular properties of food and diet to understand their impact on individuals. The genetic and molecular characteristics of individuals, along with their corresponding responses to nutrients, are measured to determine the degree of compatibility.[15] On the basis of this information, a personalized diet plan is developed that considers individual behavioral patterns, preferences, and motivations to implement effective nutrition interventions. The responses of individuals are monitored and adjusted to achieve precision nutrition.[19] Target-specific nutrition plays a crucial role in precision nutrition by controlling and delivering food nutrients and bioactive compounds to specific organs of interest.

This review aims to provide an overview of recent advancements in precision nutrition, with a particular focus on target-specific nutrition achieved through

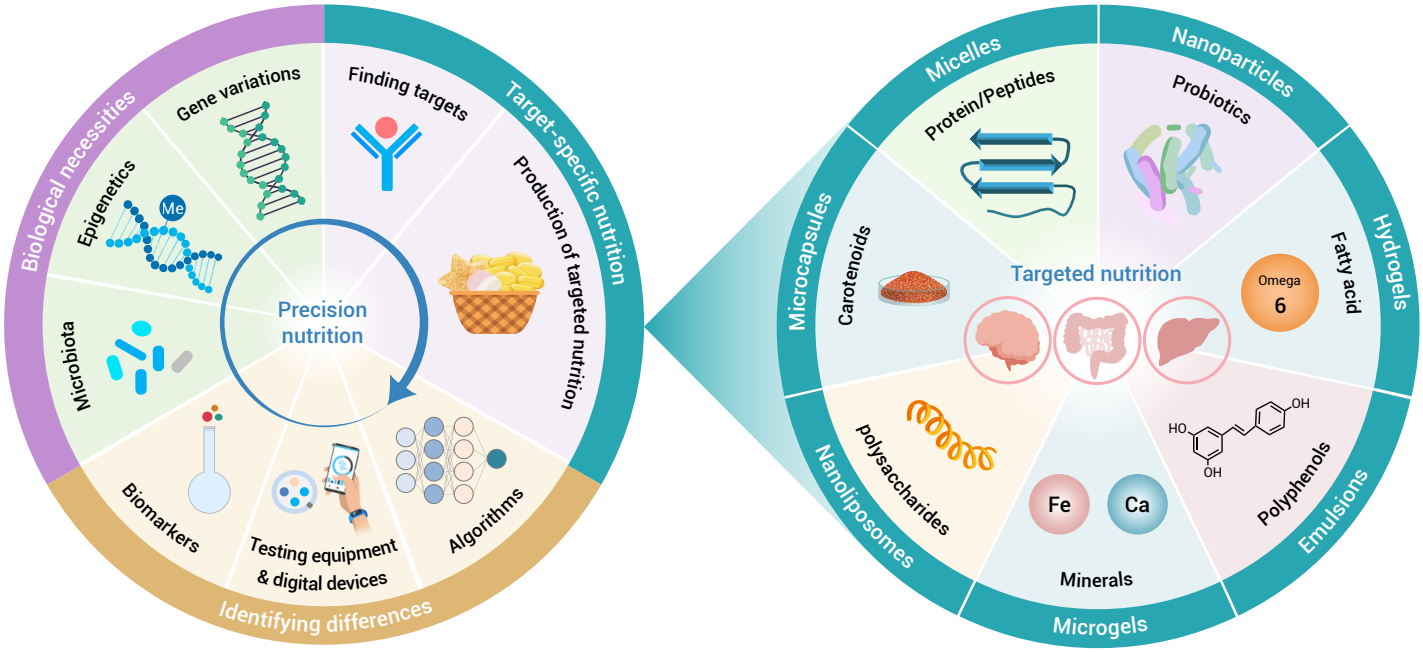

Figure 1. Overview of precision nutrition: biological foundations, interindividual differences, and target-specific nutrition Target-specific nutrition encompasses various delivery systems, such as nanoparticles, hydrogels, emulsions, microgels, nanoliposomes, and microcapsules.

the controlled delivery of proteins/peptides, probiotics, fatty acids, polyphenols, vitamins, enzymes, and carotenoids (Figure 1). Initially, we discuss the biological foundations of precision nutrition and explore the roles of genetic, epigenetic, and microbiota profiles. Next, we delve into modern technologies for identifying interindividual differences via selective biomarkers that reflect individuals' health status. Additionally, we introduce portable testing equipment and digital devices that aid in the collection of individual-specific biomarkers. Furthermore, various algorithms designed to handle individual-specific information are described. We emphasize the importance of identifying protein targets and discovering suitable nutrients as fundamental aspects of designing target-specific nutritional strategies. Finally, we outline the current challenges and future prospects of target-specific nutrition in the context of precision nutrition.

BIOLOGICAL NECESSITIES FOR PRECISION NUTRITION

Genetic profiles

The design of gene-specific nutrients relies on the gene sequences that are closely associated with individual-specific nutrient requirements. The influence of genotype on nutritional metabolism and needs has been a significant focus of research in the field of nutrition.[20] Single nucleotide polymorphisms (SNPs) refer to variation in DNA sequences observed within a population. Each individual possesses polymorphic sites, with an average of at least 50,000 SNPs in their genetic code. Alterations in a single nucleotide, such as deletions, additions, or changes, can lead to modifications in transcribed RNA and subsequent protein production. These changes can lead to variations in metabolism, nutrient requirements,[5,21] and even susceptibility to toxins.[22] SNPs have the potential to influence nutrient transformation processes.

Additionally, SNPs have been linked to various diseases, with statistical correlations identifying specific gene variants associated with more than 150 hereditary conditions.[16] Phenylketonuria (PKU) is caused by mutations in the gene that encodes the hepatic enzyme phenylalanine hydroxylase. Individuals with PKU need to avoid consuming foods rich in phenylalanine and certain amino acids.[23] Moreover, SNPs in glutathione S-transferases (GSTs) and phase II xenobiotic-metabolizing enzymes can increase the risk of certain diseases. The GSTT1 null genotype, for example, is associated with an increased risk of lung cancer in Asian populations through a meta-analysis of 23 studies.[24] Variants of other enzymes within the GST family, including GSTO1 and GSTO2, have been linked to cataract development and affect the conversion of the vitamin C precursor into its active form.[25] Consequently, individuals with these variants should be cautious in their intake of vitamin C.[22]

Gene-diet interaction analysis in a randomized controlled trial revealed that higher epithelial sodium channel genetic variation was associated with a greater reduction in systolic blood pressure following a low-sodium salt intervention.[26] Besides, a prospective cohort study indicated that inverse association between a diet high in total antioxidant capacity and the incidence of inflammatory bowel disease, with the association being most pronounced among individuals at high genetic risk and in mutation carriers of endogenous antioxidant enzyme gene SOD2 (rs4880).[27] Furthermore, in the Nurses' Health Study and replication cohorts, the association between unhealthy diet and gout risk was more pronounced among women at the higher genetic risk.[28]

Epigenetic profiles

Although cells share the same genetic code, they present diverse functions in different tissues due to epigenetic regulation.[21] Epigenetic mechanisms define heritable variation in gene expression potential without altering the core DNA sequence. These mechanisms involve noncoding RNAs, covalent modifications of histone proteins, and DNA methylation at CpG dinucleotides, which serve as epigenetic markers.[29] Epigenetic dysregulation has been associated with various diseases, including pancreatic ductal adenocarcinoma.[30]

Nutrients play a role in influencing epigenetic regulation, contributing to individual variation in responses to the same food or specific nutrients. Nutrigenomic studies have focused on understanding how food components and nutrition impact gene expression, proteins, and metabolites.[31] Food components and nutrients can directly or indirectly affect gene activity, regulating inflammation and proliferation in individuals with cancer.[5,18,32]

The influence of nutrition on epigenetic changes involves processes such as DNA methylation and the inhibition of histone deacetylation. DNA methylation typically represses gene transcription,[21] and epigenetic events modify DNA without altering the nucleotide sequence.[5] Methyl donors, including B vitamins, S-adenosyl-L-methionine, choline, and epigallocatechin, can influence epigenetic regulation. As a phytochemical, sulforaphane, which is derived from cruciferous vegetables, enhances histone acetylation, regulating cellular signals and ultimately preventing cancer in animal model and *in vitro* studies.[32] The field of nutrigenomics is still evolving, and further exploration in this area can advance precision nutrition.[33]

Microbiota profiles

In addition to differences in dietary consumption, genotype, and epigenet-

ics, variation in the host microbiota also play a role in host metabolism. The human gastrointestinal tract accommodates approximately 10^{13} gut microbiota, which possess a gene content more than 100 times greater than that of the human genome. The gut microbiota contributes to the maintenance of the gut mucosal barrier and prevents the colonization of pathogens by competitively acquiring nutrients and colonization sites in the gut.[7,14] Factors such as host age, ethnicity, and sex influence the composition of the gut microbiota. Additionally, lifestyle, medication history, dietary intake, exercise, and host behaviors also impact the abundance of the microbiota.[5]

The gut microbiota often accesses nutrients before the host,[21] and food can influence the microbiota composition. For example, long-term and short-term dietary patterns exert different effects on the microbiota. Prolonged consumption of fiber and omega-3 fatty acids may increase microbiota diversity and promote the growth of beneficial fermenters, whereas a low-fiber diet may reduce microbiota diversity. Rapid changes in diet can affect the microbiota within a few weeks but not permanently.[32] The function of gut microbes can be regulated and altered through supplementation with prebiotics and probiotics.[5,13] The interactions between food and the gut microbiome are highly personalized, as the intake of food within the past five days has a differential impact on the microbiome composition of the future in an exponential decay manner through the method of integrating fecal shotgun metagenomes and 24-h food records from 34 healthy human subjects collected daily over 17 days.[34] Therefore, when predicting the current microbiome, it is essential to consider previous dietary intake.

The gut microbiota plays a crucial role in regulating host digestion, absorption, metabolism, immunity, inflammation, and tumorigenesis, making it a virtual organ with wide-ranging effects. In fact, the gut microbiota contributes to a broader diversity of interpersonal responses than does human genetics.[20,32] Microbiota information is also crucial in assessing the host's health status. Certain microbes, such as *Prevotella copri* and *Blastocystis* spp., serve as favorable indicators of postprandial glucose metabolism while the composition of the microbiome can predict various cardiometabolic blood markers, including fasting and postprandial glycemic, lipemic, and inflammatory indices.[35] Besides, by producing metabolites, the microbiota serves as a source of nutrients for the host. For example, it synthesizes essential vitamins such as B and K. Additionally, the microbiota produces neurochemicals and signaling molecules. For example, the inhibitory neurotransmitter gamma-aminobutyric acid produced by bacteria is associated with antianxiety and antidepressant effects.[14,36] Microbiota-derived metabolites such as short-chain fatty acids (e.g., acetate, butyrate and propionic acid) and secondary bile acids also exert various effects on individuals.[37] Acetate served as a metabolic immunomodulator in breast cancer, potentiating T cells effector function and thereby supporting antitumor immunity which was verified *in vitro* and animal studies.[38] Butyrate, a microbiome-derived product notably from *Faecalibacterium*, was depleted in the feces of acute myeloid leukaemia patients. Conversely, restoring butyrate by direct supplementation or *Faecalibacterium* administration postponed the progression of acute myeloid leukaemia in mice.[39] Besides, early-life antibiotic treatment depleted hepatic butyrate, which impaired IL-18 production in both hepatocytes and Kupffer cells, resulting in the decreased mitochondrial activity and suppressed functional maturation of liver-resident natural killer cells, while dietary supplementation with *Clostridium butyricum*, a butyrate-producing human gut symbiont, rescued the impairment.[40] Furthermore, inoculating gnotobiotic mice with selected bacteria which could produce beta-hydroxybutyrate, conferred post-infarction cardiac protection.[41] By means of propionic acid production, inulin-enriched *Megamonas funiformis* ameliorated metabolic dysfunction-associated fatty liver disease.[42] Secondary bile acids, which are derived from primary bile acids by specific gut microbes, ameliorate intestinal inflammation in murine colitis models partly through the TGR5 receptor.[43] However, microbial metabolites can also have harmful effects on the host. For example, p-cresol, a uremic toxin, is derived from the aromatic amino acids phenylalanine and tyrosine by intestinal microbes.[14]

Metagenome-wide association studies primarily seek to uncover relationships between the microbiome and human diseases, such as obesity, type 2 diabetes, rheumatoid arthritis, liver cirrhosis and colorectal cancer. The progression from identifying microbiome-disease associations to delineating the microbiome's specific functional mechanisms as a causality conclusion, requires a hierarchy of experiments including animal models, *in vitro* studies and studies of longitudinal cohorts.[44] Fecal microbiota transplantation aims at restoring a healthy intestinal microbial community by transferring healthy donor fecal microbiota into a recipient's gastrointestinal tract to treat various intestinal diseases including but not limit to inflammatory bowel disease and short bowel syndrome.[45] For example, through fecal microbiota transplantation in mice model of atopic dermatitis, gut microbiota restored and atopic dermatitis-induced allergic responses were suppressed.[46] The goal of precision nutrition is to optimize the gut microbiota through dietary interventions or supplements to reduce the risk of disease.[23]

Other profiles

Certain individuals experience food allergies, with the most rapid allergic reaction being the IgE-mediated response triggered by accidental consumption of specific allergens such as peanuts, wheat, fish, and shellfish. For example, allergens such as β-parvalbumin in fish or tropomyosin in shellfish can cause such reactions. Additionally, children with food allergies may face challenges related to undernutrition and growth impairment. Therefore, precision nutrition plans should consider avoiding allergenic triggers and selecting suitable nutritional alternatives.[47] In individuals who have underlying disease, it is beneficial for them to undergo dietary interventions for a specific period. For example, the intake of leucine should be restricted in patients with isovaleric acidaemia, whereas the use of histidine supplements can increase the treatment efficacy for acute lymphoblastic leukemia.[2]

The chrono-nutrition connect the relationship between circadian rhythms, eating pattern and health. Circadian rhythms modulate metabolic physiology, including core body temperature, hormone secretion, plasma metabolite concentration and resting metabolic rate. For instance, high-energy breakfasts and low-energy lead to admirable metabolic responses.[48]

Ethnic and regional differences also influence the implementation of precision nutrition. It was reported that Asian groups had lower carbohydrate intakes compared to the white group in US, New Zealand and Australia.[49] It was found that dark-skinned ethnic groups exhibited a higher risk of vitamin D deficiency than the white group as the prevalence of vitamin D deficiency (< 20 ng/mL) in the United States was 20%-30% while Asian populations revealed a high prevalence of vitamin D deficiency, with 57.69% of individuals below 20 ng/mL.[50]

METHODS OF IDENTIFYING INTERINDIVIDUAL DIFFERENCES

Acknowledgments of individuals' health status *via* selective biomarkers

Inherent DNA variants, epigenetic modifications influenced by nutrients, and microbiota differences due to food interactions are the primary sources of interindividual variation. Understanding these differences is crucial for the development of precision nutrition strategies. Therefore, it is essential to identify quantitative, accessible, effective, and science-based biomarkers that can assess an individual's health status and optimize their response.[19] Traditional blood parameters, including low-density lipoprotein cholesterol, triglycerides, blood pressure, plasma glycemia,[19] and plasma insulin,[51] serve as excellent biomarkers. For example, when individuals consume various macronutrients for weight loss, fasting plasma glucose and plasma insulin are robust predictors.[52] A study demonstrated that baseline fasting plasma glucose and fasting insulin levels could predict differential weight loss as biomarkers of diet response after a 26-week diet rich in fiber, whole grains, fruits, and vegetables. Specifically, individuals with a baseline fasting plasma glucose level of 4.7 mmol/L experienced an average weight reduction of 1.42 kg compared with those on the control diet.[53]

Telomeres, complexes consisting of repeated nucleotide sequences (TTAGGG) and proteins, are another promising biomarker. Telomeres are located at the ends of chromosomes and protect genes during cell division. The length of telomeres gradually decreases with each division. Nutritional status and various nutrients, including vitamins, minerals, and bioactive compounds, can influence telomere length. Research has revealed that obese individuals tend to have shorter telomeres due to oxidative stress and inflammation. The epigallocatechin-3-gallate found in green tea can help combat oxidative stress by scavenging free radicals. Telomeres are considered potential blood biomarkers for age-related diseases, and changes in telomere length are associated with adiposity. Thus, telomeres could be valuable

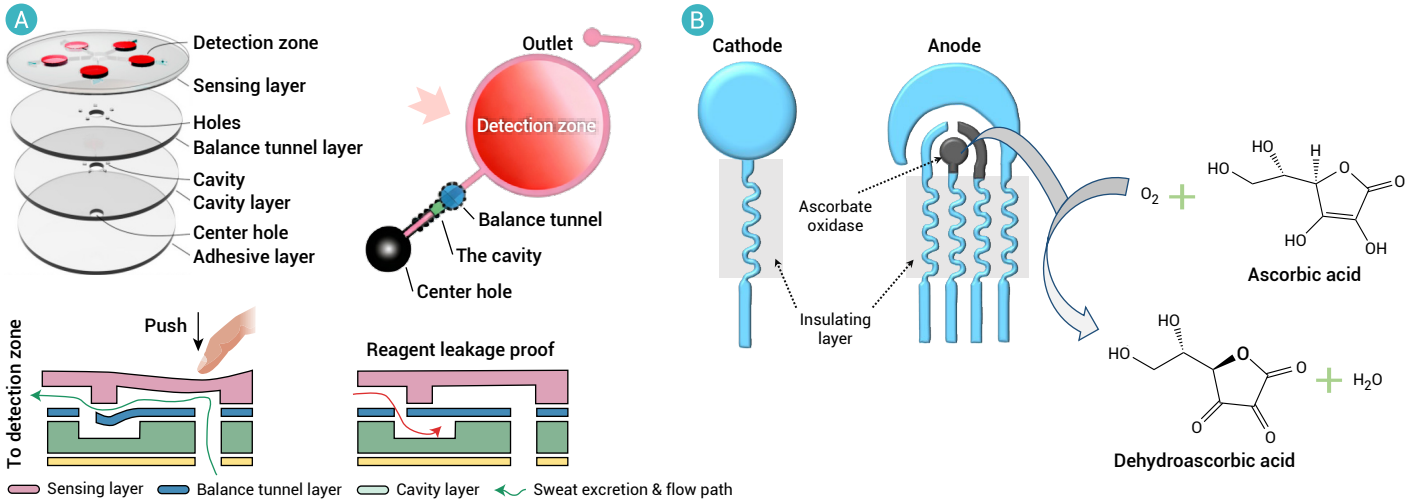

Figure 2. Portable testing equipment for individual-specific biomarker collection (A) Microfluidic chip for detecting sweat glucose.[59] Reprinted with permission. Copyright 2019, American Chemical Society. (B) Wearable sensor for noninvasive electrochemical detection of vitamin C in sweat.[60]

biomarkers of the response to obesity treatment.[54]

Furthermore, alkaline phosphatase, an enzyme that catalyzes phosphate hydrolysis, plays a crucial role in cell signaling. Among its four isozymes, intestinal alkaline phosphatase (IAP) contributes to gut microbial homeostasis and nutrient uptake. Dysfunction of the IAP is associated with persistent inflammation. Measuring the plasma IAP can be a vital parameter for assessing gut microbiota conditions and intestinal function. IAP levels can serve as an inflammatory biomarker to predict diseases such as intestinal dysbiosis and obesity.[55]

Collecting individual-specific information

Clinical testing in a hospital setting is the conventional approach for collecting biomarkers. However, outside of clinical settings, the emergence of smart electronic devices and wearable technology presents new opportunities for managing health.[56] Some researchers are developing onsite and cost-effective testing equipment as alternatives to laboratory-based testing. It has been suggested that finger blood, saliva, urine, and stool samples can be utilized for individual testing at home.

Furthermore, sweat contains various substances, including sodium, potassium, lactate, pyruvate, amino acids, glucose, and vitamins, which can serve as biomarkers. These biomarkers derived from sweat can aid in disease diagnosis, reflect physiological health, and assess nutritional balance.[57] Researchers have developed a highly integrated sensing paper that incorporates MXene/methylene blue active materials, conducting electrodes, and hydrophobic protecting wax, enabling real-time sweat analysis. Different functional areas are printed on a paper substrate and folded into a multilayer structure, allowing the paper's hydrophilic properties to efficiently collect human sweat and facilitate vertical diffusion through capillary action. This unique three-dimensional structure minimizes fluid accumulation, reduces discomfort at the human–device interface, and ensures that sensors receive immediate sweat samples rather than accumulated sweat. A dual-channel electrochemical sensor was constructed to simultaneously detect glucose and lactate, with sensitivities of 2.4 nA μM^{-1} and 0.49 $\mu A\ mM^{-1}$, respectively.[58]

Moreover, a microfluidic chip has been developed with built-in check valves to facilitate the collection of sweat into a detection reservoir. The reservoir contains glucose oxidase, peroxidase, and o-dianisidine, enabling the colorimetric detection of sweat glucose (Figure 2A). The check valves prevent any potential backflow of sweat or chemical reagents within the microchamber. With five microchambers providing parallel determinations in a single detection, the colorimetric results of sweat glucose can be visualized via a smartphone. Sweat glucose undergoes oxidation by glucose oxidase, resulting in the production of H_2O_2. Through the catalytic action of peroxidase, H_2O_2 subsequently oxidizes colorless o-dianisidine, leading to the generation of a red-colored oxidized o-dianisidine. The intensity of the color is directly proportional to the concentration of sweat glucose, with a linear range of 0.1–0.5 mM and a limit of detection of 0.03 mM.[59]

A wearable point-of-care biomarker patch has also been developed to collect and detect human sweat efficiently for measuring pH, glucose levels, and lactate concentrations. This device exhibits high sensitivity and achieves a detection range of 50–300 μM for physiological glucose concentrations, providing valuable indicators for diabetes.[57]

Additionally, the wearable sensor can detect vitamin C in sweat through noninvasive electrochemical detection (Figure 2B). This is achieved by oxidizing ascorbic acid to dehydroascorbic acid, which is catalyzed by the enzyme ascorbate oxidase, which is immobilized on the sensor. Ascorbate oxidase offers a more selective response than does nonenzymatic voltammetric detection. An increase in the vitamin C concentration corresponds to increased oxygen depletion. The reduction current of oxygen can be measured to determine the depletion of oxygen. The wearable sensor aids in monitoring changes in vitamin C levels and provides instant feedback regarding vitamin C deficiency.[60]

Handling individual-specific information via various algorithms

Artificial intelligence in discovering biological processes and predicting meals. Learning modes play a significant role in diverse applications, including the exploration of underlying biological processes and the identification of cancer subtypes. Using mRNA, miRNA, and protein profiles, DeepMF, a matrix factorization-based deep learning model, successfully revealed cancer subtypes in medulloblastoma, breast cancer, leukemia, and small-blue-round-cell cancer.[61]

To accurately assess nutrient intake from food, an algorithm based on Bayesian networks was used to calculate and classify the nutritional information of individual food items within a meal. Additionally, a 5-layer perceptron neural network was utilized to determine the nutritional balance of the meal. Furthermore, on the basis of the previous meal, the system provides suggestions for the next meal.[62] Importantly, nutrient information from a single meal is insufficient for long-term health, and the usual intake over weeks or months should be considered when designing the next meal. Integrating information on the host genotype, gut microbiota, diet history, exercise behavior, blood parameters, and anthropometric data through machine learning algorithms can potentially predict food patterns that reduce inflammation and maintain the gut microbiota balance.[18]

However, machine learning and deep learning models are often considered "black boxes", as their inner workings may lack clear meaning and interpretability. Fortunately, efforts have been made to elucidate and interpret machine learning techniques for geneticists, aiming to provide better understanding and transparency.[63]

Designing nutrition plans for people in clusters. In the field of data mining, the clustering method is employed to identify similarities among a vast amount of information and group subjects accordingly. For example,

patients were categorized into three clusters on the basis of their integral risk grades, which were calculated via gene polymorphism data. The presence of a homozygous disease pattern (A/A) was assigned a risk score of 2, a heterozygous pattern (C/A) was given a score of 2, and a homozygous safe pattern (C/C) was assigned 0 points. This study focused on 14 marker genes, including GSTM1, NBPF3, and APOA5. GSTM1 is involved in xenobiotic biotransformation, whereas NBPF3 and APOA5 indicate a risk of decreased vitamin concentration in the body. Notably, the GSTM1, NBPF3, and APOA5 genes significantly contribute to the risk of hereditary diseases in a specific cluster. As a result, individuals in this cluster benefit from a nutrition plan enriched with vitamin E. In another cluster, where there was a risk of serotonin deficiency, a diet including offal, calcium, and magnesium was recommended to increase serotonin levels.[16]

Designing personalized nutrition plans on the basis of different genetic risk scores can effectively reduce the prevalence of vitamin D deficiency and improve individual health. Genes encoding the human group-specific component (GC) vitamin D-binding protein and cytochrome P450 family 2 subfamily R polypeptide 1 have shown genome-wide associations with the 25-hydroxyvitamin D concentration, a reliable biomarker for vitamin D status. Two SNP (rs4588 and rs10741657) were selected from each locus to develop a genetic risk score. The participants were provided with information about their genetic risk, serum 25-hydroxyvitamin D concentration, and dietary and vitamin D supplementation instructions. Between August and November, the average serum 5-hydroxyvitamin D concentration increased from 64.4 ± 20.9 nmol/L to 68.5 ± 19.2 nmol/L (P = 0.006). Furthermore, the difference in serum 5-hydroxyvitamin D concentrations between participants with no risk alleles and those with 3 or 5 risk alleles decreased from 20.7 nmol/L to 8.0 nmol/L (P = 0.0063).[64]

DESIGNING TARGET-SPECIFIC NUTRIENTS FOR PRECISION NUTRITION

Clarifying protein targets and finding suitable nutrients

Nutrients can be selected to reduce the risk of disease by either activating or inhibiting specific proteins. Virtual screening technology, a cost-effective method for preliminary screening, allows researchers to identify suitable nutrients from a large-scale database on the basis of known key proteins involved in disease development.[65] In this section, we highlight the practical applications of virtual screening in the discovery of protein-targeting nutrients.

Human pancreatic amylase plays a crucial role in starch digestion and is a target for preventing type 2 diabetes. Inhibiting human pancreatic amylase helps regulate postprandial blood glucose levels. However, the FDA-approved drug acarbose is associated with gastrointestinal side effects. Therefore, the identification of a human pancreatic amylase inhibitor without side effects is essential for controlling postprandial blood glucose and preventing type 2 diabetes. Through virtual screening and enzyme activity assays, malvidin 3-O-arabinoside was identified as a potential inhibitor of human pancreatic amylase. Molecular dynamics studies revealed that the inhibitory effect resulted from the stable hydrogen bond formed between malvidin 3-O-arabinoside and the critical catalytic residues Arg195 and Asp197 of human pancreatic amylase.[66]

Individuals with blood glucose levels exceeding 200 mg dL^{-1} are often diagnosed with diabetes mellitus. Lowering postprandial glucose levels as a therapeutic approach involves preventing the breakdown of oligo- and disaccharides and slowing down their subsequent absorption. Two specific enzymes, α-amylase (αA) (EC 3.2.1.1) and α-glucosidase (αG) (EC 3.2.1.20), which are located in the small intestinal brush border, are responsible for breaking down oligosaccharides and disaccharides into monosaccharides. Inhibiting these enzymes can delay the digestion of starch and sugar, leading to reduced glucose absorption and a gradual increase in postprandial plasma glucose levels. However, certain commercial drugs, such as α-glucosidase inhibitors, lack selectivity and may cause severe gastrointestinal side effects. By employing molecular docking and virtual screening techniques on 26 polyphenols, potential α-glucosidase enzyme inhibitors, such as caffeic acid, curcumin, cyanidin, daidzein, epicatechin, eriodictyol, ferulic acid, hesperetin, naringenin, pinoresinol, quercetin, resveratrol, and syringic acid, were identified. Additionally, catechin, hesperetin, kaempferol, silibinin, and pelargonidin are speculated to be α-amylase inhibitors.[67]

Angiogenesis involves the migration and proliferation of endothelial cells to form new blood vessels in the human body. However, cancer cells promote the production of angiogenesis activators while suppressing angiogenesis inhibitors to ensure a sufficient blood supply to the tumor microenvironment. Vascular endothelial growth factor (VEGF) is a key factor in tumor angiogenesis, and the receptor VEGFR-2 plays a significant role in this process. Small tyrosine kinase inhibitors are commonly used in clinical treatments to block the angiogenesis pathway. These inhibitors bind to the ATP binding pocket and prevent the phosphorylation of the intracellular domain of VEGFR-2. Through docking simulations and molecular dynamics studies, luteolin and apigenin demonstrated the greatest potential for inhibiting phosphorylation.[68]

Angiotensin-converting enzyme and dipeptidyl peptidase IV are two membrane peptidases with distinct physiological roles. Inhibiting angiotensin-converting enzyme helps control hypertension, while inhibiting dipeptidyl peptidase IV has antihyperglycemic effects. By employing virtual screening and molecular docking techniques, tripeptides with inhibitory properties, namely, Ala-Asp-Phe, Met-Ile-Arg, and Phe-Gly-Arg, were identified from eggs. The half-maximal inhibitory concentration (IC50) values of Ala-Asp-Phe, Met-Ile-Arg, and Phe-Gly-Arg against angiotensin-converting enzyme were 27.75 mM, 24.97 mM, and 66.98 μM, respectively. For dipeptidyl peptidase IV, the IC50 values of the three inhibitory tripeptides were 16.83, 4.86, and 46.22 mM, respectively.[69]

Another source of bioactive substances also inhibits dipeptidyl peptidase IV. After four screening steps and a final *in vitro* test, O-ethyl-4-[(α-l-rhamnosyloxy)-benzyl] carbamate was identified as the most potent inhibitor among the components of Moringa oleifera Lam., with the IC50 of 798 nM. This finding provides a starting point for further research into the molecular mechanisms underlying the antidiabetic efficacy of Moringa oleifera Lam.[65]

3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) is a key enzyme involved in controlling the rate of cholesterol biosynthesis in the mevalonate pathway. Clinical trials have shown that inhibiting HMGR can significantly reduce cholesterol levels and decrease mortality risk by 22%.[70] A pharmacophore model identified an HMGR inhibitory peptide with the sequence Val-Phe-Val-Arg-Asn.[71] However, it is important to note that the effects of nutrients on targets are limited compared with those of drugs.

Phosphoinositide-3-kinase-δ (PI3Kδ) plays a regulatory role in IgE-mediated allergic diseases. Selective inhibitors of PI3Kδ can help reduce allergen-induced airway inflammation in individuals with hypolipidemia. However, some PI3Kδ inhibitors have unexpected adverse effects. Therefore, the search for safe and effective bioactive substances is highly important. Through a 3D pharmacophore model and molecular docking, ginkgoneolic acid was identified as an inhibitor of PI3Kδ with an IC50 of 2.49 μM.[72]

Taken together, these results demonstrate that specific nutritional components can interact with target proteins, particularly enzymes, thereby inhibiting their activity and reducing their occurrence.

Production of targeted nutrition

In practice, bioactive compounds derived from food exhibit various beneficial effects, such as antioxidative, antihypertensive, antihyperlipidemic, and antitumor effects.[73] However, these compounds often encounter challenges related to their sensitivity to light, heat, oxygen, low pH, and enzymes. Thus, researchers have focused on enhancing the stability and bioavailability of bioactive compounds by employing core–shell biopolymer nanoparticles.[74,75] Several factors influence the characteristics of nanoparticles. For example, the shape of nanocarriers plays a crucial role in overcoming the barriers of the intestinal mucus layer. Among them, soft, short nanotubes composed of an amphiphilic α-lactalbumin peptide that encapsulates curcumin demonstrated the highest cellular uptake and curcumin bioavailability.[76] Furthermore, the selective targeted delivery of nutrients encapsulated in nanocarriers is a practical approach to cater to the specific needs of particular organs in certain cases.

Targeted Strategies for the Brain. Capsaicin is a highly specific agonist of transient receptor potential vanilloid subtype 1 (TRPV1). The activation of TRPV1 has shown the potential to reverse neurofunction in a mouse model of focal cerebral ischemia/reperfusion. To increase the utilization of capsaicin, mesoporous iron oxide nanoparticles were employed as carriers (refer to Table 1). These nanoparticles can be metabolized *in vivo* and transported into the intracellular iron storage pool. Additionally, polyethylene glycol

was used to modify the iron oxide nanoparticles to extend their circulation time. To achieve brain targeting, lactoferrin was further modified. These distinctive features of the nanoparticles contribute to protection against cerebral ischemic injury following cardiac arrest.[77]

The utilization of nanocarriers increases the permeability and bioavailability of bioactive substances that can penetrate the blood–brain barrier and perform multiple functions within gliomas. Furthermore, tumor cells exhibit a significantly greater concentration of glutathione (GSH) than normal cells do (100–1000 times greater). Hence, a redox-triggered system was developed using disulfide bonds, which can be reduced to thiols by GSH (Figure 3A). By binding to CD44 receptors, hyaluronic acid enables glioma targeting through CD44-mediated endocytosis. Consequently, a carrier consisting of a Tween 80-modified hyaluronic acid-disulfide bond-curcumin conjugate was designed and loaded with curcumin to alleviate brain gliomas in mice bearing gliomas. Notably, Tween 80 attracts apolipoprotein E (apoE) to the plasma, which facilitates the transport of nanocarriers into the brain through low-density lipoprotein receptor-mediated endocytosis.[78] Importantly, further exploration is needed to evaluate the effects of these findings in humans, considering the differences between humans and rodents.

Furthermore, Alzheimer's disease, a neurodegenerative disorder, is characterized by dementia, memory loss, behavioral changes, and a severe decline in learning ability. It can lead to anxiety, disruptive behavior, depression, and hallucinations. The progression of Alzheimer's disease is associated with the accumulation of amyloid-β peptides in the brain and the hyperphosphorylation of the tau protein. While the blood–cerebrospinal fluid barrier and blood–brain barrier act as protective barriers for the brain, they also limit the effectiveness of therapeutic approaches against Alzheimer's disease. To overcome this challenge, nanocarriers have been extensively utilized as specialized delivery systems that can penetrate the blood–brain barrier and enhance efficacy.[79] The transferrin receptor, a transmembrane glycoprotein, is overexpressed in neurons and facilitates their cellular uptake. Lactoferrin, a naturally occurring milk-derived protein and a member of the transferrin family, takes advantage of the overexpressed lactoferrin receptors on brain endothelial cells to cross the blood–brain barrier via lactoferrin receptor-mediated transcytosis. Conjugated linoleic acid, an eighteen-carbon polyunsaturated fatty acid, has demonstrated neuroprotective effects against neuropsychiatric diseases.[80] Hence, amphiphilic micelles composed of lactoferrin and conjugated linoleic acid were constructed via carbodiimide conjugation. Conjugated linoleic acid served as the hydrophobic core, whereas lactoferrin formed the hydrophilic corona. These micelles exhibited improved *in vivo* biodistribution in brain tissue and enhanced anti-Alzheimer's disease effects in an $AlCl_3$-induced Alzheimer's disease animal model.[79] However, it is essential to gather evidence from human studies to validate the value of micelles rather than relying solely on animal models.

Another approach for achieving targeted effects involves the use of a small peptide, KLVFFAED, which selectively targets the receptor for advanced glycation end products (RAGE) that is upregulated on blood–brain barrier neurons and microglia during Alzheimer's disease (Figure 3B). Curcumin, known for its antioxidative abilities, was loaded into the core of the designed micelles. The phenylboronic groups incorporated in micelles respond to oxidative stimuli, allowing targeted delivery and reactive oxygen species (ROS)-responsive behavior, thereby alleviating Alzheimer's disease.[81]

Targeted strategies for the liver. Quercetin has demonstrated antioxidant and liver-protective effects. To increase their water solubility and bioavailability, liposomes were utilized in an animal model of acute liver injury. To achieve liver-targeting capabilities, galactosylated chitosan is attached to liposome surfaces through electrostatic absorption, leveraging the specific interaction between the asialoglycoprotein receptor and galactose residues.[82] Additionally, quercetin-loaded alginate nanogels containing glycyrrhizin were employed to enhance liver-targeted effects in acute liver failure (Figure 4A).[83] Importantly, these studies were conducted in animal models, and further investigation is needed to ascertain their relevance to humans.

In addition, astaxanthin is also known as a superior antioxidant. An astaxanthin-loaded system with lactobionic acid modified with 2-hydroxypropyl-β-cyclodextrin as a carrier exhibited good liver-targeting and antioxidant effects, as lactobionic acid has a high affinity for asialoglycoprotein receptors overexpressed in liver cells.[84] Moreover, on the basis of a liver-targeted system, (3-carboxypropyl) triphenylphosphonium bromide was introduced to achieve mitochondrion-targeting abilities, further promoting the ability of astaxanthin to provide precision nutrition against ethanol-induced oxidative stress (Figure 4B).[85]

Nonalcoholic fatty liver disease is a metabolic syndrome characterized by excessive fat accumulation in the liver due to a high-fat diet. It poses a significant challenge because it can progress to fibrosis and hepatocellular carcinoma and is associated with type 2 diabetes and cardiovascular diseases. Consequently, the identification of substances that can selectively ameliorate nonalcoholic fatty liver disease is urgently needed. Resveratrol, a bioactive polyphenol derived from natural sources such as red rapeseed, shows promising effects in reducing lipid accumulation and attenuating insulin resistance in the liver. However, its poor bioavailability limits its therapeutic potential, as it is rapidly metabolized in the gastrointestinal tract. To address this issue, researchers have explored the encapsulation of resveratrol into the hydrophobic core of hydrolyzed lysozyme micelles through self-assembly. In an animal model, liver-specific targeting was achieved by attaching a D-(+)-galactose-conjugated oxidized starch polymer to resveratrol nanocarriers via electrostatic interactions. D-(+) galactose selectively recognizes overexpressed asialoglycoprotein receptors in hepatic parenchymal cells. Once the receptor recognizes D-(+) galactose, hepatocytes internalize the entire nanocarrier, releasing resveratrol into the cytoplasm. Administering D-(+)-galactose-conjugated nanocarriers for six weeks improved lipid deposition in mice fed a high-fat diet. This effect was attributed to the modulation of the AMPK/SIRT/FAS/SREBP1c signaling pathway and downregulation of IRS-1 phosphorylation at Ser307, highlighting the potential of resveratrol-loaded nanocarriers to reverse nonalcoholic fatty liver disease at an early stage.[86]

Targeted Strategies for the Kidney. Diabetic nephropathy, a microvascular complication of both type 1 and type 2 diabetes mellitus, is characterized by glomerular and renal tubular lesions, resulting in a decreased glomerular filtration rate, glomerulosclerosis, renal tubular epithelial cell damage, and tubulointerstitial fibrosis. Upregulation of glucose transporter 1 in glomerular mesangial cells stimulated by high blood glucose suggests the potential for targeted interventions using glucose-ligand-modified molecules. The inhibition of reactive oxygen species has emerged as an effective approach to mitigate the progression of diabetic nephropathy. Compared with vitamin C and glutathione, astaxanthin, a fat-soluble natural carotenoid, has superior antioxidant properties. However, its limited bioavailability limits its therapeutic potential. To overcome this challenge, glucose ligand-modified liposomes have been developed to encapsulate astaxanthin, increasing its bioavailability and facilitating targeted delivery to the kidneys, thus alleviating diabetic nephropathy.[87]

Acute kidney injury, a life-threatening condition characterized by impaired kidney function, tubular apoptosis, and necrosis, disrupts the elimination of metabolic waste from the blood and disturbs the fluid–electrolyte balance. Curcumin, known for its remarkable antioxidant and anti-inflammatory properties, is promising for inhibiting the progression of acute kidney injury. To increase its water solubility, bioavailability, and targeted efficacy, renal-targeted polymeric micelles were formulated. P-selectin, a membrane glycoprotein, plays a role in kidney protection during acute kidney injury. Consequently, P-selectin was identified as an ideal target for effective treatment. Fucoidan, a marine polysaccharide, selectively binds P-selectin. Thus, curcumin-loaded micelles incorporating octenyl succinic anhydride-grafted fucoidan were developed as nanoplatforms for kidney-targeted delivery, aiming to inhibit the progression of acute kidney injury.[88] Furthermore, the mitochondrion-targeted peptide SS-31 has antioxidant effects and protects the kidney against oxidative stress-induced damage. As the CD44 receptor is overexpressed in the kidney during acute kidney injury, hyaluronic acid, which selectively targets the CD44 receptor, was incorporated into nanopolyplexes along with SS-31 and chitosan, providing a means for kidney-specific delivery.[89]

Targeted Strategies for the Intestine. Certain diseases exhibit slight changes characterized by the overexpression of specific receptors in tissues or organs, enabling their identification or recognition through targeting moieties and receptors. Inflammatory bowel disease (IBD), which encompasses ulcerative colitis and Crohn's disease, is a gastrointestinal mucosal immune response disorder. Ulcerative colitis, a chronic and recurrent inflammatory condition affecting the colon, leads to impairment of the colonic

Table 1. Summary of the production of targeted nutrition.

Bioactive ingredients	The composition of carriers	Pattern	Preparation methods	Treatment/Function	Targeting Mechanism	Stage of Research
Capsaicin[77]	Lactoferrin, iron oxide, polyethylene glycol	Nanoparticles	Heat reaction	Ischemic brain	Receptor-mediated	Animal model
Curcumin[78]	Tween 80, hyaluronic acid, disulfide bond, curcumin	Micelles	Self-assembly	Brain glioma	Redox-sensitive, receptor-mediated	Animal model
Linoleic acid[79]	Lactoferrin, linoleic acid	Micelles	Solvent evaporation method	Alzheimer's disease	Receptor-mediated	Animal model
Curcumin[81]	A peptide KLVFFAED, poly (ethylene glycol) (PEG), phenylboronic groups	Micelles	Supramolecular self-assembly	Alzheimer's disease	Receptor-mediated, reactive oxygen species (ROS)-responsive	Animal model
Quercetin[82]	Lactobionic acid, chitosan, cholesterol, lecithin	Liposomes	Thin-film hydration method	Acute liver injury	Receptor-mediated	Animal model
Quercetin[83]	Glycyrrhizin, alginate	Nanogels	Nanoemulsion method in high shear homogenization	Acute liver failure	Receptor-mediated	Animal model
Astaxanthin[84]	2-Hydroxypropyl-β-cyclodextrin	Nanoparticles	Self-assembly	Liver targeting	Receptor-mediated	Animal model
Astaxanthin[85]	2-Hydroxypropyl-β-cyclodextrin, sodium alginate, (3-carboxypropyl) triphenylphosphonium bromide	Nanoparticles	Self-assembly	Liver and mitochondrion targeting	Receptor-mediated	Animal model
Resveratrol[86]	Oxidized starch, hydrolyzed lysozyme, D- (+) galactose	Nanoparticles	Mixing	Nonalcoholic fatty liver disease	Receptor-mediated	Animal model
Astaxanthin[87]	Yolk lecithin, cholesterol, glucose-PEG600-DSPE	Liposomes	Thin film hydration method	Diabetic nephropathy	Receptor-mediated	Animal model
Curcumin[88]	Fucoidan, octenyl succinic anhydride	Micelles	Self-assembly	Acute kidney injury	Receptor-mediated	Animal model
SS-31 peptide[89]	Hyaluronic acid, chitosan	Nanopolyplexes	Electrostatic interaction	Acute kidney injury	Receptor-mediated, pH-responsive	Animal model
Curcumin[90]	Hyaluronic acid, gelatin, carboxymethyl chitosan	Hydrogels	Mixing	Intestinal diseases	pH-Responsive	Animal model
6-shogaol[91]	Natural-lipid	Nanoparticles	Using liposomes extruder with a 200 nm polycarbonate membrane	Inflammatory bowel disease	Passive targeting	Animal model
Astaxanthin[92]	Caseinate, sodium alginate, chitosan, triphenylphosphonium	Astaxanthin-loaded cauliflower-like carriers	Self-assembly	Ulcerative colitis	pH-Responsive	Animal model
Astaxanthin[93]	Rhodamine 123, sodium alginate, poly (propylene sulfide)	Nanoparticles	Ultrasonic-assisted self-assembly	Colitis	Receptor-mediated, ROS-triggered, pH-responsive	Animal model
Astaxanthin[94]	Whey protein isolate, (3-carboxypentyl) (triphenyl) phosphonium bromide, dextran, hyaluronic acid, lipoic acid	Nanoparticles	Double emulsion solvent evaporation	Colitis	Receptor-mediated, glutathione (GSH)-responsive	Animal model
Procyanidins[97]	Hyaluronic acid, stearic acid, cystamine dihydrochloride, (5-carboxypentyl) (triphenyl) phosphonium bromide	Nanoparticles	A double emulsion solvent evaporation technique	Inflammatory bowel disease	Receptor-mediated, GSH- responsive	Animal model
Curcumin[98]	Silk fibroin, chondroitin sulfate	Nanoparticles	Sonicating and mixing	Ulcerative colitis	Receptor-mediated, ROS- responsive, GSH-responsive, pH-responsive	Animal model
Curcumin[99]	Chondroitin sulfate, poly (lactic acid-co-glycolic acid), chitosan	Nanoparticles	Using an emulsion solvent evaporation technique	Ulcerative colitis	Receptor-mediated	Animal model
Quercetin[100]	De-esterified yuzu peel pectin, oligochitosan	Hydrogel beads	Ionic gelation methods	Delivering to the colon	Simulated colonic fluid-responsive	*In vitro*
Pelargonidin-3-O-glucoside[101]	Soybean lecithin, cholesterol, pectin, chitosan	Nanoliposomes	Thin film-rehydrated methods	Suitable for colon-targeted delivery	Simulated colonic fluid-responsive	*In vitro*
Fucoxanthin[102]	Shellac	Nanoparticles	A simple microfluidic strategy	Releasing fucoxanthin in simulated colonic fluids	pH-Responsive	*In vitro*
Lactobacillus Plantarum strain[103]	Alginate, Ca, EDTA, Whey protein isolate, (−)-epigallocatechin-3-gallate, polyglycerol polyricinoleate	W1/O/W2 double emulsions	Under low consumption method with two-step emulsification	For probiotics colon-targeted release	pH-Responsive	*In vitro*

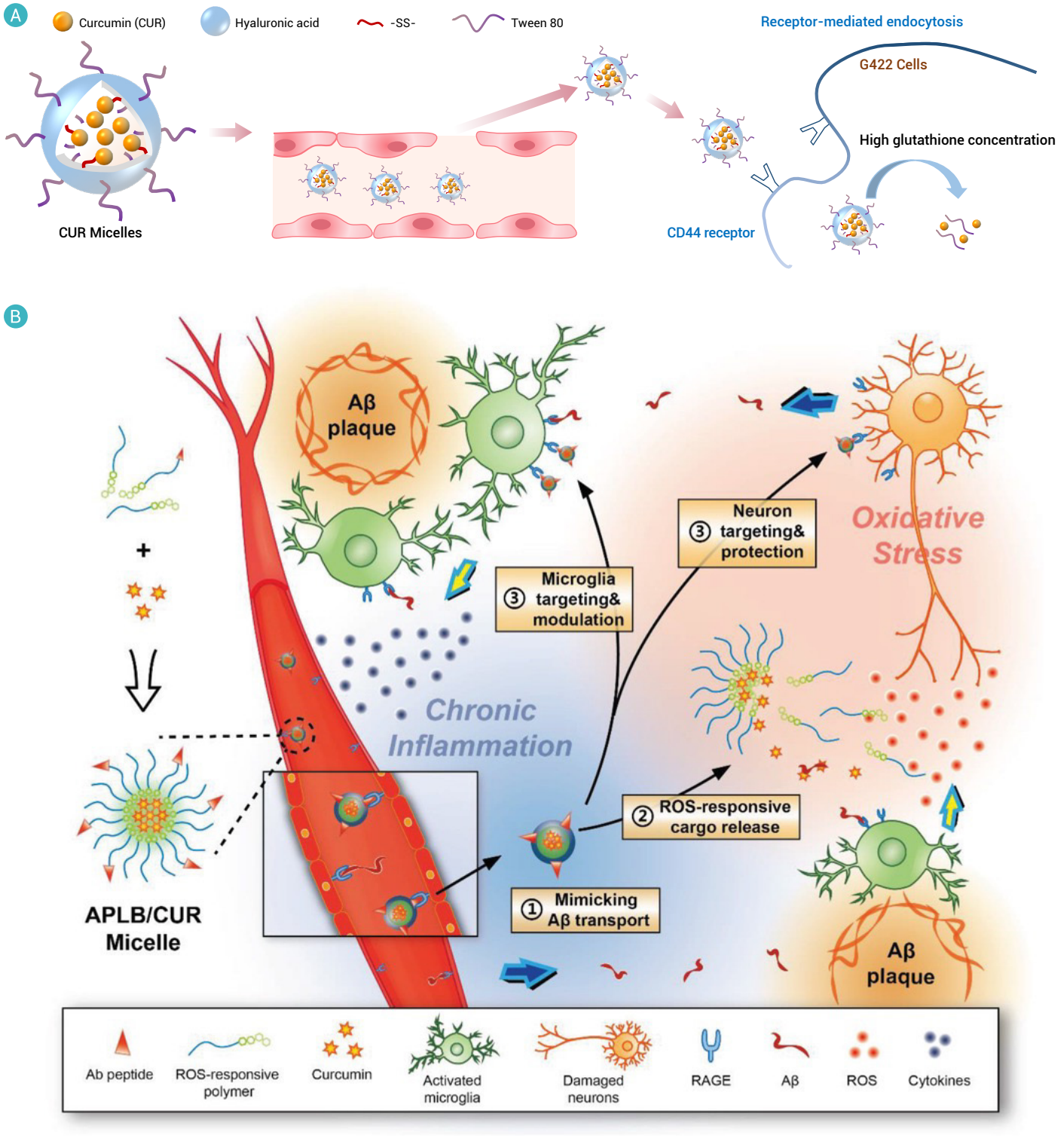

Figure 3. Targeted Nutrition for Brain Disorders (A) Schematic representation of a Tween 80-modified hyaluronic acid-disulfide bond-curcumin conjugate loaded with curcumin designed to alleviate brain glioma.[78] (B) ROS-responsive micelles loaded with curcumin, demonstrating their potential in ameliorating Alzheimer's disease.[81] Reprinted with permission. Copyright 2018, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

mucosal barrier and poses challenges for treatment. CD44, a transmembrane glycoprotein that is overexpressed on activated macrophages in colitis tissues, has been identified as a specific receptor. Consequently, the development of disease-targeted delivery systems utilizing bioactive food compounds for nutritional intervention in ulcerative colitis has garnered significant attention.

Disease-targeting strategies involve passive and active targeting, including loading, targeted delivery, and controlled release of bioactive materials into microspheres or nanocarriers. In the context of passive targeting, numerous studies have focused on nutrient delivery to ameliorate UC. Curcumin, a natural polyphenol, and carboxymethyl chitosan were utilized to fabricate microspheres. These microspheres, which incorporate an innovative addition of phosphoric acid, demonstrated effective delivery of curcumin, along with its antioxidant properties. To further enhance the efficacy of curcumin in the colon, carboxymethyl chitosan microspheres were embedded within hydrogels composed of hyaluronic acid and gelatin. Pharmacokinetic experiments

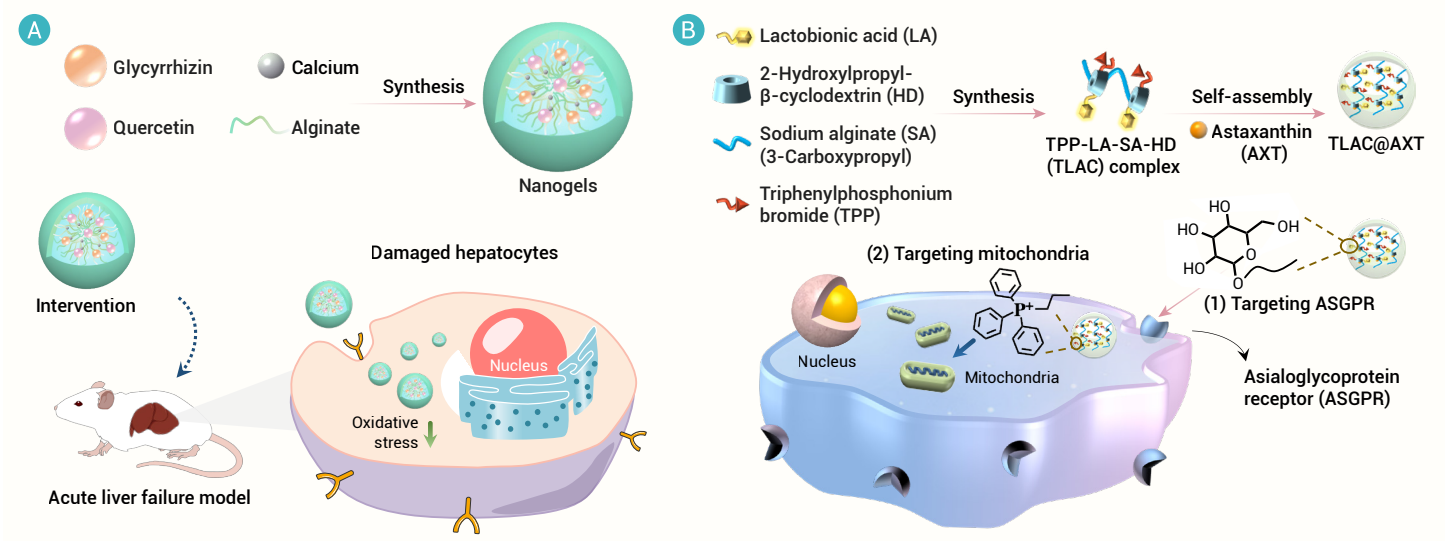

Figure 4. Production of targeted nutrition for the liver (A) Quercetin-loaded alginate nanogels with glycyrrhizin for alleviating acute liver failure.[83] (B) Astaxanthin-loaded nanoparticles for liver and mitochondria targeting to relieve oxidative stress.[85] Reprinted with permission. Copyright 2023, Elservier Ltd.

in vivo indicated that the combination of microspheres and hydrogels sustained high levels of curcumin in colon tissue for over 24 hours, providing benefits for colitis treatment.[90]

Ginger, a widely used spice and dietary supplement, has favorable effects on reducing colitis. 6-Shogaol, an active hydrophobic phenolic component in ginger, exhibits antioxidative and anti-inflammatory activities. However, its rapid metabolism results in concentrations in target tissues that fall below therapeutic levels *in vitro*. To address this issue, ginger lipid nanoparticles were developed for the efficient delivery of 6-shogaol to the colon. Compared with those of 6-shogaol alone, the metabolites of 6-shogaol, including a cysteine-conjugated metabolite and a glutathione-conjugated metabolite, demonstrated superior anti-inflammatory effects.[91] Traditional oral tablets or capsules suffer from nonspecific biodistribution and uncontrollable release. Upon oral administration, nanoparticles tend to accumulate in colitis tissues, partly due to disruption of the mucosal barrier and impaired epithelial tight junctions in ulcerative colitis. This phenomenon, referred to as the "epithelial enhanced permeability and retention (eEPR) effect," enables nanoparticles to passively deliver bioactive substances to colitis tissues. However, the therapeutic efficacy of nanoparticles in this context is still below expectations.

Astaxanthin, a fat-soluble xanthophyll carotenoid with remarkable antioxidant and anti-inflammatory properties, was incorporated into cauliflower-like carriers with the ability to target mitochondria to relieve UC. The amphiphilic structure of caseinate stabilized astaxanthin, and chitosan and sodium alginate exhibited pH-responsive functions, protecting astaxanthin under acidic conditions.[92] In addition, to alleviate colitis, rhodamine 123, a mitochondrion-targeting molecule, sodium alginate, and poly(propylene sulfide), a reactive oxygen species (ROS)-responsive group, are used as carriers to load astaxanthin (Figure 5A).[93] Moreover, the use of astaxanthin, which is an orally deliverable nanoparticle with macrophage affinity, mitochondrion-targeting ability and glutathione-triggered function, is also outstanding for alleviating UC (Figure 5B) .[94]

Procyanidins, known for their exceptional antioxidant, anti-inflammatory, intestinal barrier protection, and gut microbiota modulation activities, are considered promising compounds for active targeting in IBD alleviation.[95,96] However, their bioavailability is significantly limited by oxygen, free radicals, and pepsin. To overcome these challenges, nanoparticles composed of hyaluronic acid, procyanidins, stearic acid, cystamine dihydrochloride, and 5-carboxypentyl (triphenyl) phosphonium bromide have been developed. Disulfide bonds within the nanoparticles provided a reduction-sensitive function, whereas 5-carboxypentyl (triphenyl) phosphonium bromide served as a mitochondria-specific delivery molecule. These nanoparticles offer a glutathione-responsive and dual-targeting approach for effectively alleviating IBD.[97]

Chondroitin sulfate (CS), a negatively charged polysaccharide, is also a ligand for CD44.[98] Thus, functionalizing nanoparticles with CS was shown to be beneficial for enhancing endocytosis to alleviate UC. In addition to CS, curcumin, known for its attractive antioxidant, anti-inflammatory, and relatively safe properties, was incorporated into the nanoparticles. These curcumin-loaded nanoparticles, comprising natural silk fibroin and CS, demonstrated enhanced cellular uptake capacity and improved bioavailability of curcumin. The controlled release of curcumin was achieved through pH/H_2O_2/GSH stimulation, facilitated by the disruption of the β-sheet structure and disulfide bonds in silk fibroin.

Another study utilized CS to target the glycoprotein CD44.[99] Poly(lactic acid-co-glycolic acid), an FDA-approved biocompatible polymer, was employed. By functionalizing the nanoparticles with CS and encapsulating curcumin, higher cell internalization efficiency and improved therapeutic outcomes against ulcerative colitis were achieved compared with those of nontargeted carboxymethyl cellulose nanoparticles.

Hydrogel beads were prepared via the ionic gelation method using de-esterified pectin from yuzu peel and oligochitosan. The formation of hydrogel beads relied on the formation of a polyelectrolyte complex between the carboxyl groups (-COO^-) of de-esterified pectin and the ammonium groups (-NH_3^+) of oligochitosan, as well as cross-linking involving the carboxyl groups (-COO-) of de-esterified pectin and calcium ions (Ca^{2+}). When exposed to simulated gastric and intestinal fluid, the cumulative release of quercetin from the hydrogel beads was less than 1%. However, in the simulated colonic fluid, the hydrogel beads significantly released quercetin (ranging from 65.37% to 99.54%) over 12 hours. This demonstrated that the hydrogel beads effectively achieved controlled release of quercetin in the colon.[100]

Pelargonidin-3-O-glucoside, a water-soluble pigment and a beneficial anthocyanin with anti-inflammatory, antidiabetic, and cytoprotective properties, has limited bioavailability due to its susceptibility to pH and enzymatic effects in the gastrointestinal tract. To target the colon, nanoliposomes functionalized with pectin and chitosan were developed to encapsulate pelargonidin-3-O-glucoside. These functionalized nanoliposomes demonstrated excellent thermal stability and acid resistance. After simulated enzymatic and nonenzymatic digestion in the small intestine, approximately 47.5% and 57.5% of the pelargonidin-3-O-glucoside content, respectively, was retained by the functionalized nanoliposomes, indicating their suitability for colon delivery.[101]

Fucoxanthin, a naturally occurring pigment derived from brown algae, possesses anti-inflammatory properties and provides protection to the colon. To achieve targeted delivery to the colon, shellac nanoparticles loaded with fucoxanthin have been developed. The nanoparticles ranged in size from 100–200 nm. *In vitro* experiments demonstrated that the nanoparticles effectively shielded fucoxanthin from simulated gastric and intestinal fluids while facilitating its release in simulated colonic fluids.[102]

Probiotics, such as *Lactobacillus*, *Bifidobacterium,* and gram-positive

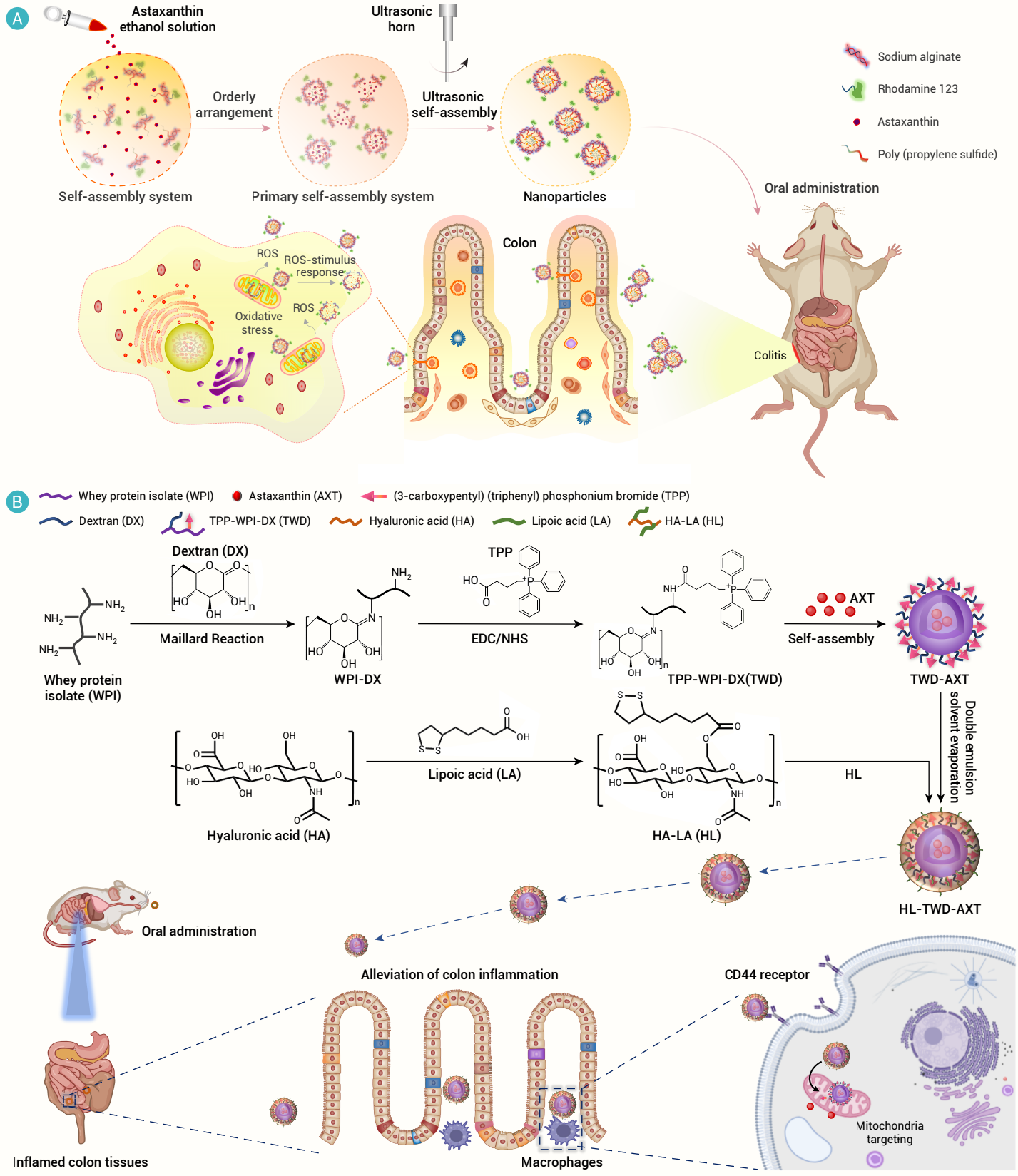

Figure 5. Production of targeted nutrition for colon delivery (A) Astaxanthin-loaded nanoparticles with mitochondrion-targeting and ROS-responsive abilities alleviate colitis.[93] Reprinted with permission. Copyright 2022, Elservier Ltd. (B) Mitochondrion-targeting and glutathione-triggered nanoparticles with macrophage affinity to relieve colitis.[94] Reprinted with permission. Copyright 2022, Elservier Ltd.

cocci, play a beneficial role in enhancing the balance of the gut microflora and inhibiting the growth of pathogens. However, the viability of probiotics can be compromised during processing and oral administration, resulting in insufficient viable probiotics reaching the colon. To address this issue, W1/O/W2 double emulsions were developed as carriers to encapsulate *Lactobacillus plantarum*, a representative probiotic, in the W1 phase. Polyglycerol polyricinoleate, an edible lipophilic surfactant, served as the inner W1/O stabilizer, whereas whey protein isolate and covalent conjugate nanoparticles of (−)-

epigallocatechin-3-gallate were employed as the external O/W2 stabilizers. The W2 phase contained EDTA, calcium, and alginate and was pH sensitive. At pH values below 4.0, calcium can dissociate from the Ca-EDTA chelate and interact with the G residues of alginate to form hydrogels. Conversely, under neutral pH conditions, calcium could dissociate from the Ca-alginate hydrogel, transforming the hydrogel into a solution. This formulation provides a colon-targeted release carrier for individuals requiring supplementation with the Lactobacillus plantarum strain through oral administration.[103]

OBSTACLES AND DISCUSSION IN PRECISION NUTRITION

Individuals often face barriers such as a lack of knowledge, dietary noncompliance, psychological barriers and safety concerns. Research shows that 80% of Americans experience conflicting nutritional information, leading to uncertainty about their dietary choices. This uncertainty stems from unreliable sources, including media and industry organizations.[20] Nonadherence to dietary recommendations can be influenced by several factors, including time constraints, financial constraints, and difficulties in assessing the nutritional value of foods. Many individuals find it difficult to follow dietary guidelines due to time constraints, especially young people, who prioritize academic obligations, work responsibilities, and recreational activities over maintaining a balanced diet. Additionally, while individuals may have basic knowledge about healthy eating, they often struggle with portion estimation and food group categorization.[104]

Psychological factors, such as anxiety, depression, and emotional stress, can markedly affect physical activity and dietary habits, thus compromising the effectiveness of dietary interventions. Therefore, dietary interventions need to consider individual preferences and methods to support adherence.[105] In addition, individuals often express concerns about the safety and confidentiality of genetic test results.[106] Accurately measuring an individual's dietary intake is challenging and time-consuming. However, the emergence of smart camera apps and digital tools that use food image recognition and natural language processing offers user-friendly solutions and reduces the burden of data entry. This technology has notably improved the accuracy and precision of dietary intake assessments, addressing the challenges individuals face in estimating food portion sizes prior to consumption.[107] Nonetheless, the translation of these innovations into practice remains a significant hurdle.

Various preparation methods in preparing targeted nutrition products, including solvent evaporation, physically mixing, ultrasonic-assisted self-assembly and nanoemulsion in high shear homogenization are advantageous due to straightforward procedures and minimal equipment requirements, which confers favorable scalability for the industrial fabrication of micelles and core-shell nanoparticles. Among these, simply mixing method with low investment and energy input is particularly suitable to industrialization. Additionally, for processing targeted nutrients, thermal reactions (e.g., the Maillard reaction) may be superior to chemical catalysis, which are more aligned with the requirements of the functional food industry. Meanwhile, for the solvent evaporation method, it is advisable to use food-grade solvents to ensure biosafety and comply with market regulations.

Achieving clinal translation of targeted nutrition products requires considering biocompatibility, long-term safety, and effects of biodegradation products. Most studies focus on animal models to verify biosafety. Apart from animal models, human trials are also needed to observe biocompatibility. Furthermore, nanomaterials designed for repeated administration pose risks of bioaccumulation in body. Long-term safety trials help to better observe dysregulation of immune responses, chronic inflammation or other adverse events induced by nanomaterials. Biodegradation products of nanomaterials are also worth investigating. For instance, metabolites of 6-shogaol, specifically a cysteine conjugate and a glutathione conjugate, exhibited superior anti-inflammatory effects compared to 6-shogaol alone.[91]

To provide practical dietary guidance, it is also essential to consider effective dosages that are feasible in daily intake. For example, in a triple-blind, randomized, placebo-controlled clinical trial of 60 patients with rheumatoid Arthritis, 20 mg/day of astaxanthin for 8 weeks have effectively reduced erythrocyte sedimentation rate compared to non-intervention group.[108] In a randomized, double-blind, placebo-controlled crossover trial, 12 weeks treatment of quercetin (500 mg/day, suggested as functional food doses in the United States) could reduce intrahepatic lipid contents in patients with nonalcoholic fatty liver disease.[109] In a randomized, double-blind, placebo-controlled trial, 72 weeks administration of phospholipid curcumin (2 g/day) could improve liver histology and metabolite profile (triglycerides, fasting glucose, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) in patients with nonalcoholic steatohepatitis.[110] Importantly, the results from human trials provide critical insights for formulating dietary recommendations. With respect to research methodologies, while population-based evidence may not adequately support individual-based recommendations derived from personalized health data and external circumstances,[20] randomized controlled trials provide insights into the average treatment effect among participants but do not accurately predict individual responses. To address this challenge, n-of-1 studies on individual subjects can be conducted.[111] Furthermore, while artificial intelligence facilitates the handling of vast amounts of information, understanding the intricate interplay between genes, environmental influences, the microbiota, and host status (e.g., diseases and nutritional conditions) can lead to conflicting conclusions.[20] Therefore, fundamental research remains critical in advancing our understanding in this field.

CONCLUSIONS

Individuals respond differently to the same type of food intake due to inherent differences in metabolism that are shaped by factors such as genotype, epigenetic regulation, and microbiota composition. In addition, the diversity of dietary choices can alter the composition of the microbiota, resulting in the production of metabolites that affect the host. Identifying quantitative biomarkers that classify an individual's health status is critical for translating theory into practice. Portable devices facilitate instant metabolite sampling for analysis, whereas artificial intelligence assists in data collection and interpretation. However, despite its ability to process information, AI does not help elucidate the underlying mechanisms involved. Therefore, the limitations of precision nutrition must be recognized, and its strengths must be utilized appropriately. Research methodologies, particularly n-of-1 studies, offer a more tailored approach to individuals than traditional randomized controlled trials in precision nutrition development. In addition, the design of target-specific nutrient complexes represents a novel strategy to efficiently increase health benefits by providing controlled degradation, improved biocompatibility, and enhanced protection for vulnerable bioactive materials.

AI-driven models will be trained on individuals' multi-omics data, continuous metabolite monitoring, and recorded dietary intake, allowing for the recommendation of optimal food choices before individuals' intake. Dietary management may evolve into a proactive, autonomous health agent. This advanced system would not only track individuals' nutritional intake but also interact with personal mobile apps. It would dynamically adjust weekly meal plan based on individuals' schedule, real-time metabolic data from wearables, and personal health goals. Besides, targeted nutrition products and 3D food printing could allow for the creation of meals tailored to an individual's micronutrient needs and genetic taste perceptions on demand. Ultimately, personalized nutrition's future would hinge on the continuous feedback loop between individual's and their data, not in a one-time genetic analysis. The goal is to create a system that is predictive, preventive, and seamlessly integrated into daily life, empowering individuals to make optimal nutritional choices that are uniquely suited to their evolving biology. Translating this potential into reality necessitates a multidisciplinary collaboration among researchers, technologists, clinicians, and policymakers, with the shared goal of ensuring the efficacy, ethical integrity, and equitable accessibility of these innovations.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.