



Perspective

From food to medicine: The coarse grain paradigm shift

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1 Introduction

The Food and Agriculture Organization (FAO) of the United Nations defines coarse grains as all cereal grains except wheat and rice^[1]. This categorization puts them in opposition to the two staple cereals in world food statistics. Throughout this perspective, we adopt this FAO definition, which restricts the term "coarse

grains" exclusively to non-staple cereal crops, including but not limited to foxtail millet (*Setaria italica*), proso millet (*Panicum miliaceum*), hullless barley (*Hordeum vulgare* var. *nudum*), common buckwheat (*Fagopyrum esculentum*) and tartary buckwheat (*F. tataricum*), oats (*Avena sativa*), sorghum (*Sorghum bicolor*), maize (*Zea mays*), and other minor cereals. These crops are distinguished by high protein content and complementary

amino acid profiles, high dietary fiber, high B-complex vitamin, high mineral deposits, and functional phytochemicals such as polyphenols, flavonoids, β -glucans and anthocyanins all of which contribute to their nutritional and health promoting characteristics. Nonetheless, in the last 50 years, agricultural modernization has caused gradual marginalization of coarse grains because of reasons like their coarse texture, time-consuming preparation, and lack of industrialization. This has led to a steady reduction in their intake compared to staple foods^[2]. At the same time, the prevalence of chronic metabolic disorders, such as diabetes mellitus, obesity, metabolic dysfunction-associated steatotic liver disease, and hyperuricemia, has increased significantly worldwide. The two-fold challenge of modern medicine is that pharmacological interventions tend to focus on symptoms instead of causes whereas lifestyle interventions often have poor patient compliance. This quandary where the resources of agriculture in terms of nutrition are underutilized and yet the incidence of preventable chronic diseases is increasing, highlights the necessity to reconsider the importance of coarse grains^[3].

The use of coarse grains both in medicine and food fields is a tradition that has been firmly established in the thousands of years of Chinese civilization. The *Huangdi Neijing* brought about the concept of the five grains as nourishment, making cereals not just sources of energy but also essential building blocks to maintaining good health. *Coix* seed was acknowledged in the *Shennong Bencaojing*, which was the introduction of this coarse grain into the world of medicines^[4]. During the Tang Dynasty, the *Shiliao Bencao* described certain therapeutic effects: Millet was believed to nourish stomach *qi* and expel heat in the spleen and stomach, whereas buckwheat was believed to strengthen the gastrointestinal tract, increase physical strength, and refresh the spirit. This era marked the transition between general principles and practice of specific varieties in dietary therapy^[5]. These observations were synthesized by Shizhen Li in the *Compendium of Materia Medica*, where he observed that *Coix* seed could be used to strengthen the spleen and improve the stomach, tonify the lungs and alleviate heat, expel wind and remove dampness. These descriptions foreshadow a new idea of specific interventions. The textual evidence amassed over two thousand years shows that this functional paradigm, which focuses on strengthening the spleen, removing dampness, calming the spirit, and tonifying the kidney by taking coarse grain, is not just a collection of folk cures, but an entire empirical system. This system provides a historical background to contemporary scientific inquiry.

This empirical system is effective, but has a cognitive limitation: Its effectiveness is explained by analogy and stays at the macroscopic experiential level. "*Coix* seed eliminates dampness" does not tell us which molecules interact with which targets through what mechanisms, just as "millet calms the spirit" does not tell us why people have different responses to eating the same bowl of porridge. These two levels of ambiguity have triggered a paradigm shift from empirical medicine to precision medicine. In recent years, metabolomics has allowed full coverage of metabolic fingerprint changes pre- and post-dietary interventions^[6]. Metagenomic sequencing of gut microbiota has unravelled full courses of food components modified by microbes. Network pharmacology has unraveled molecular networks for synergistic actions of multi-component and multi-target coarse grains^[7]. This integration of these three technological advances has, for the first time, enabled the traditional idea of "five grains as nourishment" to be reinterpreted while retaining therapeutic insights honed over millennia and translating them into a cognitive framework based

on quantifiable, evidence-based and computable modern scientific terms. This evolution is not so much a break from tradition as an application of historical knowledge using modern methods, transforming dietary therapy from empirical to evidence-based practice^[8].

This perspective suggests a paradigm shift in the area of food and medicine homology (FMH) and coarse grains. It proposes to change the concept of "five grains as nourishment" to "five grains as medicine". The word "as medicine" does not mean that coarse grains are drugs. Rather, it shifts their role along a spectrum. On one extreme, coarse grains are traditional food staples supplying calories and essential nutrients. In the middle, they become vehicles for dietary intervention by delivering bioactive compounds that regulate metabolism and microbiota. At the high end, they become programmable elements of precision nutrition approaches, based on individual metabolic and physiological data. This repositioning transforms coarse grains as mere passive suppliers of simple nutrition into active data-driven intervention carriers to prevent and manage chronic diseases, fundamentally transforming their functional positioning, application modalities, evaluation criteria, and industrial models. The paper will critically examine theoretical frameworks, health interventions, industrial restructuring, and technological breakthroughs in a systematic manner in various dimensions. It seeks to chart the structural changes that are likely to occur in cognitive systems, product formats, business models, and underlying technologies in the coarse grains industry in the next ten years. This work is prefigurative not in the sense of projecting far-off science fiction scenes, but in foreseeing systemic reconfigurations which have already started germinating and are unavoidable but incomplete. The goal is to establish an intellectual framework that is open to discussion, criticism, and evolution, thereby contributing to disciplinary development, industrial transformation, and policy formulation (Fig. 1).

2 Scientific decoding and evaluation system of dietary therapy

2.1 Scientific interpretation of traditional efficacy of coarse grains

2.1.1 Establishment of a metabolomics-based evaluation system for dietary therapy efficacy

The core of metabolomics-based evaluation system for nutritional and health promoting effects is to translate the traditional efficacy concepts such as fortifying the spleen and eliminating dampness into quantifiable and traceable metabolic pathway perturbation profiles, so as to realize modern biochemical characterization of empirical knowledge with a history of thousands of years. Untargeted metabolomics provides important technical support for this purpose. It can comprehensively capture the changes of metabolic fingerprint profiles in human serum and urine before and after nutritional interventions without predefining research hypotheses, thus revealing panoramic mechanisms by which food components perturb the body's metabolic network. This technology has been strictly verified in many fields. For example, researchers integrated serum and urine metabolomics data to identify specific metabolic pathway perturbations caused by exogenous substance exposure, providing evidence that metabolic profiles in body fluids could sensitively

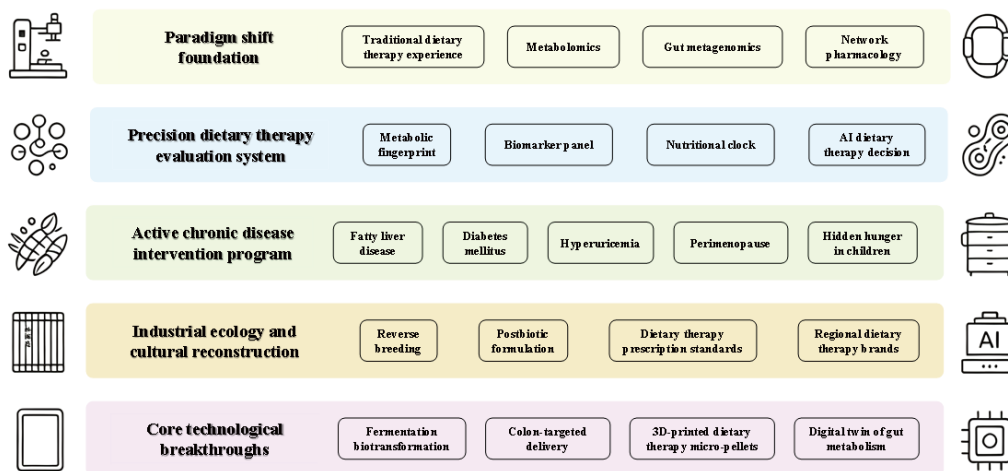


Figure 1 From food to medicine: The coarse grain paradigm shift.

reflect the overall response of the body to external interventions. Metabolomics research on coarse grains with high polyphenol content has shown that various food sources have different metabolic fingerprints, which provides chemical-level guidelines to identify functional ingredients and quality control. Overall, these studies suggest that metabolomics is a sensitive approach to capturing the molecular level perturbation of the metabolic state by dietary intake.

The introduction of this technological platform to assess the efficacy of dietary therapy requires that all health claims of future FMH multigrain formulations be supported by metabolomic data. The core design involves paired serum and urine samples before and after treatment in a highly controlled clinical trial, the acquisition of extensive metabolite profiles using high-resolution mass spectrometry and then relating differential metabolites to metabolic pathways through bioinformatics approaches. This approach provides an integrated framework connecting dietary intervention, metabolite perturbations and pathway perturbations, which can provide testable hypotheses about the interactions between dietary patterns and therapeutic potential. It is worth stressing that metabolomic correlations are informative but do not alone establish clinical efficacy. Instead, they are a discovery instrument that needs to be supplemented with dose-response experiments, specific interventions and finally clinical endpoint validation. Focusing on the example of fortifying the spleen, its modern scientific definition can be associated with the post-interventional improvements in branched-chain amino acid metabolism, regeneration of tricarboxylic acid cycle intermediates, and higher concentrations of gut microbiota-associated metabolites, all of which may indicate better mitochondrial energy metabolism efficiency and intestinal barrier integrity. On the other hand, dampness-eliminating could be defined on the metabolomic level as decreased inflammation-related lipid mediators, decreased oxidative stress markers, and normalization of water-electrolyte balance pathways. The creation of this evaluative system is important not only in terms of providing empirical evidence on traditional therapeutic effects but also in introducing a new paradigm of food product evaluation. Similar to how metabolomics has been used in rheumatoid arthritis metabolic phenotyping to enable accurate diagnosis, nutritional metabolomics will enable every multigrain formulation to have a unique metabolic perturbation signature profile. Consequently, the importance of dietary therapy might be studied more and more not just as historical documents in literature but also as

quantifiable biological reactions that can be systematically described, contrasted, and exposed to additional hypothesis testing.

In addition to metabolomics, other omics layers such as transcriptomics, proteomics and epigenomics provide additional information about the underlying mechanisms of dietary interventions. Transcriptomics can uncover diet-induced changes in gene expression profiles. Proteomics can capture protein modifications and functional changes. Epigenomics can detect diet-induced changes in DNA methylation and histone modifications that could underlie long-term metabolic responses. The integration of these multi-omics technologies has the potential to build a more holistic view of how coarse grain dietary interventions disrupt biological systems across different molecular levels.

The metabolomics-based assessment platform introduced here is a promising first step, but there are several key challenges that need to be overcome before it can be used for regulatory or clinical applications. There are no standardised procedures for sample collection, processing and data analysis, which greatly hampers data integration across studies. The majority of published metabolomics studies of dietary interventions are underpowered and do not address the large inter-individual variability. The challenge of translating the discovery of differential metabolites to causal links with clinical endpoints persists. The next steps should involve standardizing analytical workflows, creating population-specific reference metabolome databases, and planning appropriately powered intervention studies with predefined metabolomic outcomes.

2.1.2 Gut microbiota as a potential mediator of dietary therapeutic effects

The gut microbiome has been hypothesized to play a role in mediating the effects of dietary therapy, which may help reconcile traditional theories of diet with scientific evidence. There is increasing correlational and mechanistic evidence to support this hypothesis, but causal relationships in humans are yet to be determined. The impact of dietary interventions on host health depends on how gut microbes recognize, transform, and signal the active components in food. The integrated use of multi-omics technologies such as metagenomic sequencing and metabolomics enable precise tracking of changes in gut microbiota caused by dietary interventions at the species level and monitoring of host metabolic networks, establishing a complete chain of "dietary

intervention, microbiota remodeling, metabolic improvement." Fecal microbiota transplantation experiments have demonstrated that transferring donor microbiota from animals that had specific dietary interventions into germ-free or antibiotic-depleted recipient animals effectively recapitulates the improvements in glucose and lipid metabolism induced by the dietary intervention, indicating that gut microbiota changes play a causal role in this specific animal model, suggesting that the microbiota is not merely an epiphenomenon in the context of these dietary interventions. Whether this necessity holds across different dietary contexts and in human populations requires further investigation. Gut microbiota ferment and break down dietary fibers and other food-derived components, producing active metabolites, including short-chain fatty acids, secondary bile acids, and tryptophan derivatives. These metabolites act through the gut-liver axis and the gut-brain axis to engage key metabolic sensors and nuclear receptors in the liver, adipose tissue, pancreatic islets, and the central nervous system, thereby achieving systemic regulation of host glucose and lipid metabolic homeostasis. Non-polysaccharide active ingredients in complex dietary therapy systems such as traditional Chinese medicine (TCM) formulas can only improve metabolic disorders such as spleen deficiency syndrome with the help of gut microbiota. Once antibiotics wipe out the microbiota, these protective effects are significantly weakened. The gut microbiome is not merely a bystander in diet-based health effects. It is a key mediator that carries dietary signals, amplifies their effects, and precisely transmits them to the host's various physiological systems. In the future, predicting individual responses to dietary interventions based on baseline gut microbiota profiles holds promise for shifting dietary strategies from a one-size-fits-all approach towards precision and personalization.

2.1.3 Establishing a food-nourishing biomarker database

Among coarse grains, highland barley, oats, buckwheat, millet, and quinoa should not be understood merely as sources of energy. They are dietary carriers of beta-glucans, resistant starch, flavonoids, polyphenols, gamma-aminobutyric acid (GABA), anthocyanins, minerals, and other bioactive components. The purpose of a food-nourishing biomarker database is therefore not to reduce traditional functions such as spleen-strengthening or dampness-removing to one laboratory indicator. Rather, it should place nature and flavor, meridian tropism, processing, compatibility, dose, intake timing, constitution status, and modern multi-omics endpoints within the same evidence framework. This is more consistent with the logic of FMH: Foods are a source of daily nourishment, but also of repeated and relatively low-level molecular insults that alter host metabolism, microbiota and chronic inflammation.

In practical terms, the database should follow a four-layer structure: Traditional description, clinical phenotype, molecular endpoint, and detectable biospecimen. spleen-strengthening should not be represented only by motilin or gastrin. It should be evaluated together with appetite, abdominal distension, stool pattern, fatigue, postprandial glucose fluctuation, GLP-1, bile acids, short-chain fatty acids, amino acid profiles, and microbial fermentation capacity. Dampness-removing should not be represented only by lower inflammatory cytokines. It should also include heaviness sensation, sticky stool, fluid metabolism, intestinal barrier function, lipid deposition, hs-CRP, IL-6, TNF- α , LPS/LBP, AQP-related water transport signals, and microbiota-derived metabolites. Evidence on flavonoid-related MAPK and NF-

kappaB regulation, diet-driven tuning of immune-cell ferroptosis thresholds, and microbial metabolites as cross-system mediators all suggests that dietary therapy should be interpreted through biomarker panels rather than single readouts.

The next task is to move from observable association to reproducible evidence. Each candidate biomarker should be linked to sample type, analytical platform, sampling time, pre-analytical handling, dietary exposure record, syndrome scale, and minimal clinically important difference, and should be retested in controlled interventions, real-world cohorts, and wearable-device-based longitudinal monitoring. For forward-looking coarse-grain research, the most useful database will not be a static ingredient table, but a dynamic knowledge base that can answer which constitution and metabolic background, after which grain or compatible formula, leads to directionally consistent and clinically meaningful biomarker shifts.

The proposed integration of TCM concepts (nature and flavor, meridian tropism, and constitution status) with modern multi-omics endpoints within a unified biomarker framework raises a fundamental methodological tension. TCM operates within a holistic and dynamic paradigm, wherein health and disease are understood as emergent properties of the whole organism in interaction with its environment, whereas modern molecular biomedicine operates predominantly within a reductionist paradigm that seeks to identify discrete causal factors and linear pathways. Our proposed integration strategy acknowledges this tension and does not attempt to reduce TCM concepts to single molecular surrogates. Instead, we treat multi-omics profiles as providing a set of molecular descriptors that can be correlated with, but not substitute for, the holistic diagnostic framework of TCM. This method has its limitations: Network pharmacology and multi-layer omics integration can provide suggestions for links between TCM patterns and molecular signatures, but it cannot fully capture the dynamic and context-sensitive nature of TCM diagnosis. We propose that the best way to proceed is not to look for a direct correspondence between TCM concepts and molecular biomarkers, but rather to consider multi-omics as an additional source of information that complements, rather than supplants, the conventional approach.

2.2 Precision quantification from population to individual

2.2.1 Constructing a Chinese population dietary-metabolomic reference atlas

The accurate assessment of the dietary therapy of coarse grains should be based on the dietary and metabolic profiles of the Chinese people. The staple-food structure, cooking practices, extent of refining grains, regional ecology, ethnic genetic background, urban-rural lifestyle, workload, seasonal eating patterns, and chronic-disease spectrum vary significantly among Chinese residents. Direct importation of external reference ranges can lead to misdiagnosis of normal regional variation as pathological deviation, or underestimation of early metabolic drift in high-risk subgroups. A Chinese population dietary-metabolomic reference atlas must then have two purposes: To define localized normal ranges and to explain why individuals react differently to the same food-nourishing intervention.

Multicenter, longitudinal and stratified cohorts should be used to construct the atlas. Food-frequency data, coarse-grain intake, food-medicine homologous compatibility, nature-flavor-meridian

and constitution information, anthropometry, clinical biochemistry, serum and urine metabolomics, lipidomics, fecal microbiota, inflammatory markers, and wearable measures (sleep, physical activity, continuous glucose profiles) should all be present in core data layers. Stratification should go beyond age and sex to include region, ethnicity, BMI, urban-rural residence, season, circadian rhythm, glycemic and lipid status, fatty-liver risk, and family genetic background. Studies on young-onset diabetes show that genetic factors, lifestyle, and environmental exposures jointly shape metabolic heterogeneity. Therefore, genetic risk and lifestyle exposure should be modeled together rather than treating diet as an isolated variable.

The final value of this atlas is not simply to label a marker as high or low. It should determine whether an individual has deviated from the metabolic trajectory of their own population and constitution subgroup, and then predict the probability of response to spleen-strengthening, dampness-removing, glucose-lowering, lipid-regulating, or sleep-supporting dietary goals. A practical route is to begin with high-frequency coarse grains and high-burden chronic conditions, establishing exposure markers, metabolic-effect markers, and safety boundaries for highland barley, oats, buckwheat, millet, and quinoa, before extending to different regions, syndromes, and life-course populations. Only when the reference atlas is connected to the biomarker database can coarse-grain FMH move from experience-based recommendation to quantifiable, stratified, and iteratively optimized precision nourishment.

2.2.2 Establishment of a research framework for dietary therapy response heterogeneity

Interindividual variability in response to ostensibly identical food-based or FMH interventions is striking and fundamentally reflects the complexity of the host-microbiome-environment interaction network. Within the emerging framework of precision nutrition, this heterogeneity is increasingly understood as the integrated consequence of host genetic background (for example, polymorphisms that modulate nutrient-sensing and metabolic pathways), baseline gut microbiota composition (which constrains the fermentative capacity for specific dietary substrates and the resulting metabolite profiles), and lifestyle factors such as habitual dietary patterns, physical activity, sleep and psychosocial stress. A landmark study has demonstrated that postprandial glycemic responses to the same foods vary by several-fold between individuals and can be accurately predicted by models that incorporate gut microbiome features alongside clinical and lifestyle variables. More recently, bidirectional crosstalk between host epigenetic regulation and the intestinal microbiome has been proposed as an additional layer of plasticity that further shapes nutritional responses over time. These insights underscore the need to build an explicit "response heterogeneity" framework for food-based interventions that integrates multi-omics profiling (genome, metagenome, metabolome) with high-resolution lifestyle monitoring, in order to develop computational models capable of predicting individual responses and answering the fundamental question of why the same dietary regimen yields divergent outcomes across individuals.

2.2.3 Development of the chrono-nutrition clock theory

Circadian rhythm, an endogenous timing system evolved in organisms, regulates metabolic, immune, and neural functions with a periodicity of approximately twenty-four h. This regulation is driven by rhythmic oscillations in gene expression, which are

controlled by transcription-translation feedback loops. Recent studies have revealed important interactions between meal timing and the circadian system at multiple levels. Molecularly, feeding times can reprogram hepatic diurnal gene expression patterns, independent of the liver's endogenous clock, implying that "when to eat" is a powerful chronobiotic agent. Metabolically, alignment between meals and biological clocks affects fluxes in energy substrate metabolism. Restricted feeding during early time windows improves glucose metabolism and insulin sensitivity, whereas late feeding impairs metabolic processes. Moreover, dietary rhythms are correlated with risks of biological aging across organs, with later last meals linked to increased risks of accelerated aging in both heart and liver tissues. These results highlight the need to take into account the temporal aspect of nutrient intake in optimizing dietary regimens, in addition to nutrient type and amount.

The theory of the "chrono-nutrition clock" is based on the human circadian rhythm as a key factor in designing dietary formulations. It suggests that the efficacy of the same nutritional combinations can vary greatly depending on the time of day they are ingested, and requires an accurate three-dimensional match between certain time windows, metabolic targets, and nutrient compositions. Three levels of hierarchical support are needed to apply this theory with evidence-based support. To define absorption windows and periods of effects of different bioactive components, chronometabolic dynamic profiles of major coarse grains and nutraceutical substances should be constructed first. Secondly, optimal overlapping times between clock-sensitive stages of target tissues and nutrient signaling input times to specific health goals need to be determined. For instance, promoting high-resistant starch cereals during breakfast can boost their second-meal effect, and recommending GABA-rich cereals for dinner can coincide with endogenous sleep-promoting signals. The third level takes into account the variability of clock gene polymorphisms. There is evidence that clock gene polymorphisms (such as *CLOCK*) affect metabolic responses to dietary schedules and obesity. This highlights the need for individualization in the "chrono-nutrition clock". Through the combination of personal genotypes, circadian rhythms and metabolic goals, time-segmented nutritional strategies will transform nutritional approaches from fixed ingredient-focused to dynamic time-window-driven strategies. This is a key step forward in personalized nutrition, shifting from "thousand persons, thousand faces" to "one person, thousand times" time optimization.

The concept of "one person, thousand times" chrono-nutrition is an attractive long-term vision, but there are several key challenges that need to be addressed before it can be realized. The most important challenge is the lack of throughput for real-time metabolic analysis. Existing technologies only detect a small subset of metabolites, resulting in significant knowledge gaps regarding dynamic metabolic events. Second, the scalability of inter-individual predictive models is problematic: Models developed in one population do not necessarily translate well to other populations because of genetic, habitual dietary and microbiome differences. Third, the frequent data acquisition needed for individualized chrono-nutrition places a heavy compliance burden on users, calling into question the feasibility and fairness of such strategies. The best hope for addressing these challenges is the emergence of minimally invasive, multi-target biosensors coupled with federated learning approaches that can harness data from various populations while maintaining privacy. But considerable effort will be needed to develop and validate these technologies at

scale.

2.3 Technological breakthroughs in evaluation paradigm

2.3.1 Constructing an artificial intelligence decision system for food-based health preservation

The main worth of an artificial intelligence decision system of food-based health preservation is not to substitute professional judgment with algorithms, but to interrelate real-world health data with the theoretical framework of traditional Chinese dietary healthcare. The system can incorporate diet logs, constitution related attributes, symptoms, lab results, lifestyle factors and follow-up results and develop a structured body of knowledge on foods, FMH materials, nature and flavor, meridian tropism, therapeutic functions, compatibility principles and contraindications. Based on this, it is possible to create interpretable models that will aid personalized recommendations. In cases where a person presents with spleen deficiency with dampness, coarse grains like *Coix* seed (sweet, bland and slightly cold, entering the spleen, stomach and lung meridians) can be taken into consideration based on constitution and pattern differentiation. Nonetheless, individuals with spleen-stomach deficiency-cold, pregnancy, allergies or taking medication still require alerts and professional review. The system can use individual feedback and intervention results to continuously improve its recommendations and enable a shift towards population-level dietary advice to personalized food-based health-preserving choices. Its purpose should however be supportive and should not be mixed up with disease diagnosis or clinical treatment.

Although AI-assisted dietary suggestions have a lot of potential, there is not enough evidence to justify their use in clinical practice. The main constraints are the absence of rigorous prospective validation studies, standardized data governance models, and the possibility of algorithmic bias when training models on unrepresentative populations. These problems should be resolved by large-scale, prospective, multicenter validation studies and development of clear data governance procedures before the role of AI in food-based health preservation can become strictly supportive and informational, as opposed to diagnostic or prescriptive.

2.3.2 Development of wearable device-driven real-time dietary therapy adjustment

Real-time dietary intervention using wearable devices aims to combine various biosensing technologies to turn dietary advice into a dynamic feedback loop, rather than a set of static recommendations. Continuous glucose monitoring technology records real-time changes in blood glucose levels, and its use is not limited to diabetes care but also gestational glucose control and other metabolic disorders, enabling early identification of hyperglycemic and hypoglycemic episodes by high-frequency data streams. At the same time, sweat sensors can be used as a non-invasive method of monitoring metabolism by sensing different biomarkers in sweat including glucose, lactate, and uric acid. It is noteworthy that sweat glucose sensors have become able to offer real-time information that correlates with blood glucose levels without requiring blood sampling. Heart rate variability (HRV) is a sensitive measure of autonomic nervous system activity, which reflects individual stress and cardiovascular adaptation in real time, with studies showing strong correlations between dynamic HRV measures and glycemic fluctuations.

Together, these three sensing modalities record real-time physiological signals of metabolic substrates, biochemical markers in bodily fluids and neural regulation. Their multimodal data stream allows quantitative answers to the earlier experience-based question: What does the body need now?

With the ongoing accumulation of data on individual metabolic variations by multimodal sensors, the paradigm of dietary intervention changes to a closed-loop system that is dynamically iterative rather than a fixed regimen. The working principle of this closed-loop system is to analyze real-time information on glucose levels, sweat metabolites and autonomic nervous activity obtained by sensors using cloud-based algorithms, which automatically initiate proportional changes in the formulation of complex carbohydrate blends to be used in future meals. As an example, with higher amplitude of blood glucose fluctuation, the percentage of resistant starch-containing grains is high. In case of an increase in the inflammation-related metabolites, the formulation is changed to a polyphenol-rich composition based on *Coix* seed. On detecting a stress response through heart rate variability, a cereal program enriched with GABA to relax neural activity is triggered. This closed-loop system of monitoring-interpretation-intervention-remonitoring proves its worth not only in rectifying current metabolic deviations but more to the point in allowing early detection and preventive intervention of possible health hazards. As technological advances in flexible electronics, microfluidic chips, and artificial intelligence continue to occur, this dynamic dietary management model will extend beyond populations with specific diseases to general health management contexts, finally turning the theoretical idea of person-specific and time-specific precision nutrition into practice.

The closed-loop system presented above must be viewed as a technological vision on the long-term scale, and not as a clinical reality that is about to happen. At present, there are significant validation obstacles to the combination of continuous glucose monitoring (CGM), sweat sensors, and HRV data into automated dietary adjustment algorithms. The physiological signals captured by these sensors are indirect proxies for metabolic state, and their relationship to specific nutrient requirements remains incompletely characterized. The algorithms proposed to translate these signals into dietary recommendations have not been validated in prospective clinical trials. The use of closed-loop systems in dietary management raises important questions about data governance, user safety, and professional oversight, questions that must be addressed through regulatory frameworks and clinical guidelines before such systems can be deployed. We suggest that the most productive near-term applications of these technologies are in supporting human decision-making, such as providing real-time feedback to patients and clinicians, rather than in autonomous algorithmic control.

2.3.3 Establishment of an AI analysis system for mood-food diaries

The association between emotion and diet has long remained at the level of subjective experience, making quantitative analysis difficult. The core breakthrough of establishing an AI analysis system for emotion-food diaries lies in converting individually recorded daily emotional states and food intake data into computable, structured information, and uncovering hidden personalized association patterns through machine learning. This technical pathway has received support from evidence-based research. A team from Fudan University utilized massive data from campus smart meal ordering systems to construct, for the

first time, the association trajectory between dietary intake patterns and depressive symptom evolution in young populations, confirming the quantifiable link between long-term dietary patterns and mental health. In practical applications, existing systems have established mapping relationships between emotional labels and food categories, for instance, identifying preferences for specific nutrients under stress conditions. More recent studies use deep learning and natural language processing methods to infer emotional information from users' diary entries, and generate individualised diet plans that also take into account mental health issues using generative models. These systems convert subjective data into actionable data resources, driving a shift in dietary advice from population-based general recommendations to personalised feedback.

3 From nutritional support to active intervention in disease

3.1 The first line of defense in chronic disease intervention

3.1.1 Coarse grain meal replacement targeting the gut-liver axis for fatty liver disease

The pathophysiology of metabolic dysfunction-associated steatotic liver disease (MASLD) is a clear example of the vicious cycle between gut microbiota dysbiosis and hepatic lipid accumulation, thus making dietary interventions targeting the gut-liver axis the first line of defense in chronic disease treatment. Our suggested prescription is a combination of barley-derived β -glucan with the main idea of preventing the secondary hepatic insult caused by the endotoxins produced by the gut at the source. Barley β -glucan being a soluble dietary fiber has been shown to positively regulate the structure of the gut microbial community, decrease the Firmicutes-to-Bacteroidetes ratio, and limit the generation and translocation of endotoxic lipopolysaccharide into the blood. Clinical research also shows that meal replacement plans supplemented with these functional ingredients can have a significant effect on decreasing intrahepatic triglycerides and liver function biomarkers. This formula intervenes accurately at the crucial points of fatty liver development through the two-fold process of decreasing hepatic steatosis and protecting the intestinal barrier.

3.1.2 Development of a proposed framework for the "first therapeutic meal" in chronic disease management

The increased coarse grain intake has been universally recognized by international multidisciplinary experts as a cornerstone in the prevention and treatment of MASLD. This suggestion is based on the overall regulatory effects of dietary fiber, polyphenols, and certain phytochemicals in coarse grains on hepatic lipid metabolism and gut microbiota. Similarly, the Chinese diabetes lipid management consensus highlights the importance of refining the dietary patterns and increasing the amount of dietary fiber intake as the main approaches to reduce low-density lipoprotein cholesterol and cardiovascular risks. All these consensus statements have identified coarse-grain breakfasts as a combined intervention strategy. Coarse grains contain soluble fiber, resistant starch, and bioactive phytochemicals that simultaneously regulate three key pathways: Glycemic control, lipid control, and inflammation control. This

provides strong scientific evidence to take such breakfasts into account as a first line of defense against chronic diseases.

Based on the above scientific evidence, future efforts should focus on developing and advocating a proposed expert framework for the "first therapeutic meal". This framework should clearly position breakfast with coarse grains as a standard node of chronic disease prevention and management. The essence of this framework should have three components. First, it includes variety adaptation, in which individualized coarse-grain breakfast programs are adapted to various metabolic phenotypes. For example, high-resistant starch millet or oats for glycemic control, and high β -glucan highland barley for lipid control. Secondly, it sets chrononutritional proportion standards, determining minimum threshold proportions of daily carbohydrate intake for breakfast coarse grains and best time windows for maximum metabolic window utilisation. Finally, it provides personalised adaptation strategies, dynamically optimising combinations and processing approaches of breakfast coarse grains according to continuous glucose monitoring and feedback from metabolic biomarkers.

3.1.3 Design of an adjunct dietary therapy pack with synergistic effects in combination with metformin

Metformin is an effective first-line antidiabetic drug that reduces blood glucose. Nevertheless, gastrointestinal intolerance, lactic acid accumulation and other side effects are observed in some patients. In addition, monotherapy may need to be used at relatively high doses to attain the best glycemic control. Therefore, the question of how to maximize therapeutic effectiveness and minimize the dose needed and adverse effects is a crucial problem in the optimization of diabetes treatment. Recent research has shown that bioactive ingredients of certain coarse grains can have synergistic interactions with metformin *via* different mechanisms, which gives a scientific foundation to explore more about drug-food synergy in precision therapy. It has been reported that when sorghum ethanol extract and metformin were mixed in a 4:6 ratio, the consumption of glucose by HepG2 cells rose to 77% (metformin alone) and combination index (CI < 1) indicated significant synergism. In other studies as well, it has been shown that low-to-moderate concentrations of anthocyanins with metformin produced a CI of less than 0.9 *in vitro*. Combination group demonstrated significantly better outcomes in fasting blood glucose, HbA1c and HOMA-IR in diabetic mouse models compared to monotherapy.

Besides glycemic regulation, the components of coarse grain have demonstrated potential advantages in lipid metabolism and safety improvement. Red rice bran extract was discovered to reduce oxidative stress injury by scavenging free radicals and restoring superoxide dismutase and glutathione levels. Clinical issues with metformin include gastrointestinal discomfort and lactate accumulation and anthocyanin co-administration was discovered to significantly reduce blood lactate levels. Additionally, some of the components obtained through coarse grain have shown hepatoprotective properties and enhanced liver functional indicators. The results indicate that the formulations containing coarse grains, which are rationally designed, can potentiate efficacy and should be further studied in clinical trials. To conclude, coarse grains like sorghum, as well as other components of coarse grain such as red rice bran and anthocyanin-rich cereal extracts, have synergistic effects with metformin by several mechanisms, such as activation of the AMPK pathway, upregulation of GLUT4, and suppression of oxidative stress. Converting this evidence into a

clinical "companion dietary package" is a promising approach to attaining better glucose control using lower doses of drugs and fewer side effects, thus offering a new paradigm in integrated diabetes care.

3.2 Tailored coarse grain meal packages for different populations

3.2.1 Metabolic "soil amelioration" during the periconceptional period

The doctrines of the kidney governing reproduction and the spleen generating *qi* and blood generation are central to TCM which compares reproduction to soil cultivation. Periconceptional interventions are meant to remodel the maternal metabolic environment through the concept of FMH. Recent research supports the idea that classical TCM treatments with kidney-tonifying and spleen-strengthening effects can modulate gut microbiota, balance Th17/Treg immune response, and thereby improve endometrial morphology and homeostasis.

This phase follows the principle of "mild supplementation" (Ping Bu) to enhance metabolic stability and diversity of gut microbes. Oats (*Avena sativa*, sweet-flat, meridian entry: Spleen/liver) contain high-viscosity β -glucan. Randomized crossover studies demonstrate that by increasing chyme viscosity and slowing gastric emptying, oats not only blunt postprandial glucose excursions but also have a carryover effect on improving glycemic tolerance in the next meal. Foxtail millet (*Setaria italica*, sweet-salty-cool, meridian entry: Kidney/spleen/stomach) contains soluble dietary fiber in its bran layer, which after *in vitro* fermentation, selectively promotes butyrate-producing bacteria such as *Faecalibacterium* and *Bifidobacterium*, while inhibiting pathogens such as *Enterococcus*, thus regulating gut homeostasis through butyrate metabolism.

The physiological emphasis changes to nourishing the fetus and ensuring fetal vitality, which requires a therapeutic shift to harmonizing the Middle Jiao, tonifying the kidney and consolidating the fetal root. Easily digestible cereals (such as millet, barley) should be emphasized in diets to aid stomach *qi* without disrupting fetal stability. It has been shown that low glycemic load (GL) diets, especially when confounders are adjusted, contribute to the gestational glucose homeostasis and decrease gestational diabetes mellitus (GDM) risk. On the other hand, low fiber consumption increases the chances of constipation by about six times, whereas sufficient coarse grain fiber stimulates intestinal peristalsis and fecal bulk. This phase is a strict contraindication of drastic tonics and blood-mobilizing drugs to avoid disturbing the uterus.

After delivery, blood loss and hormonal changes tend to result in dual depletion of *qi* and blood. The physiological priority is changed to tonify *qi*, nourish blood, strengthen the spleen and tonify the kidney to help the uterus involute and lactate. The dietary advice prefers sweet-flat coarse grains that find their way into the spleen and kidney meridians (such as oats, millet) which replenish vitality without affecting spleen transport. Cross-sectional analyses indicate that there is a negative relationship between high-frequency consumption of coarse grain and risk of depressive symptoms. The mechanism probably underlies SCFA-mediated regulation of neurotransmitter homeostasis through the microbiota-gut-brain axis, which can provide potential advantages against early postpartum mood disorders.

The dietary recommendations for the periconceptional period,

pregnancy and postpartum are derived from a combination of TCM theories and observations. But there is a lack of rigorous randomized controlled trials specifically examining coarse grain interventions in these groups. Important data that are lacking include dose-response curves, safety data on potential antinutrient effects (such as phytic acid) and long-term maternal and child health outcomes. In the absence of this evidence, advice should be conservative and tailored, with supervision by health care providers.

3.2.2 Dietary therapy approaches for children with hidden hunger

The problem of children's "hidden hunger" is not necessarily a shortage of food, but rather a deficiency of micronutrients from unbalanced diets despite an adequate food supply. The diets of many picky eaters are low in important micronutrients like iron, zinc, vitamin A and vitamin D. Low levels of these nutrients are strongly linked to growth faltering and impaired immunity. The problem with picky eating is that it is both a nutritional and behavioral issue. Simply providing healthy foods is often ineffective as children may refuse to eat them. Research indicates that offering a greater variety of foods and enabling children to make their own choices can significantly boost vegetable intake. Moreover, the addition of high-nutrient-density foods to snacks that children already prefer can enhance their overall diet without substantially increasing their caloric intake. Thus, to deal with hidden hunger in children, it is necessary to change the approach towards what they should eat to what they want to eat rather than enforcing dietary norms strictly. This is a key principle in developing effective dietary intervention strategies.

The combination of coarse grains and FMH materials is a unique solution. These ingredients provide a nutritional foundation rich in dietary fiber, B vitamins and minerals when combined with millet, oats, buckwheat and other coarse grains to make ready-to-eat grain bars or puffed snacks. This synergy transforms snacks into more than just sources of empty calories that satisfy the taste buds but turns them into tools of active micronutrient supplementation. The future development of this field will not only be aimed at perfecting formulations but also biofortification of coarse grain varieties as an innovative approach to addressing hidden hunger worldwide. The basic nutrition of food therapy preparations can be improved already on the raw material level by using breeding methods which selectively increase the content of the main micronutrients like iron and zinc in grains. Combining biofortified coarse grain strains with FMH substances and integrating them into routine snack programs among children has the potential to become a paradigm shift in combating hidden hunger. This strategy shifts intervention measures away from passive supplementation to active, routine and sustainable alteration of dietary practices.

The hidden hunger approach proposed here is attractive but needs considerable evidence to be generated before it can be implemented. The major knowledge gaps are the bioavailability of micronutrients in biofortified coarse grains in children, palatability and acceptability of biofortified products in children of various age groups, and long-term nutritional benefits of sustained intake. We propose that future studies should focus on well-constructed intervention trials with objective nutritional outcomes.

3.2.3 Dietary management for a smooth menopausal transition

The physiological changes that occur during the menopausal transition are explained by the TCM as the exhaustion of *Tian Gui*

(the heavenly water/vital essence) and *Yin* deficiency of the liver and kidney. This is clinically evident in vasomotor symptoms (such as hot flashes, night sweats), insomnia and a reduction in basal metabolic rate. The strategy is based on the principle of FMH and promotes gentle dietary manipulation instead of aggressive pharmacological treatment.

Bound polyphenols in coarse grains are liberated *via* microbial metabolism. These bioactive compounds activate the ROS/Akt/Nrf2 signaling cascade to exert antioxidant effects. Synergizing with key commensals such as *Clostridium butyricum*, they collectively mitigate oxidative stress and alleviate dyslipidemia.

The evidence for coarse grain interventions in menopausal symptom management is limited to indirect mechanistic observations and small observational studies. High-quality randomized controlled trials with predefined menopausal symptom endpoints are urgently needed. Additionally, the optimal types, doses, and processing methods of coarse grains for this population remain to be determined.

3.2.4 Elderly health: From chronic disease management to combating loneliness

In the process of global population aging, the prevalence of malnutrition among older adults is 3.1% in community settings, 22% in hospitals, and 28.7% in long-term care facilities, and is frequently accompanied by frailty, muscle loss, cognitive decline, and mortality. With advancing age, energy requirements decline, whereas protein requirements increase. A daily intake of at least 1.0 g/kg body weight is recommended to counteract anabolic resistance and maintain muscle function. For older adults living alone who have trouble with daily tasks, oral nutritional supplements (ONS) and food fortification are recommended as convenient and effective strategies to increase energy and protein intake. Lavender aromatherapy can significantly alleviate depressive symptoms and loneliness in frail older adults, with group-based interventions yielding better outcomes. However, most nutrition intervention studies currently have low levels of evidence and face implementation challenges due to poor adherence, follow-up difficulties, and unequal resource distribution. Future efforts should strengthen high-quality randomized controlled trials and integrate psychological support and environmental factors into nutritional intervention design, thereby achieving integrated "nutritional-psychological-social" care that can offer truly effective healthy-aging solutions for older adults living alone.

3.2.5 Precision support for extreme environments and critical perioperative care

Under extreme environmental conditions, including high-altitude hypoxia, deep-sea hyperbaria, and spaceflight microgravity, organisms are subjected to multiple stressors such as hypoxia, cold, and microgravity, which induce pronounced alterations in gut microbial diversity and function, affecting metabolism, immunity, and skeletal health. To deal with the external pressures mentioned above, microbiota-supporting foods enriched with prebiotics and functional polysaccharides such as highland barley β -glucan have shown potential to modulate the gut microbiota, exert anti-inflammatory effects, and maintain bone metabolic homeostasis. Precision nutrition interventions based on gut microbiota regulation show potential for use in extreme environments and the perioperative period, but more high-quality clinical studies are needed to validate their

personalized strategies and long-term effects.

3.3 Coarse grains for the prevention of mental disorders

3.3.1 Scientific reinterpretation and enhancement of classic calming formulas

Classic formulas for calming the spirit, such as Ganmai Dazao Decoction, have been shown to exert antidepressant effects by modulating gut microbial community structure. Animal experiments demonstrate that this formula reduces the Firmicutes-to-Bacteroidetes ratio, ameliorates depressive behaviors in chronically stressed mice, and elevates cerebral serotonin levels. Further mechanistic investigations reveal that it suppresses the activation of inflammatory signaling pathways in the cerebral cortex, reduces the expression of pro-inflammatory cytokines, and regulates tryptophan metabolic homeostasis, thereby increasing brain serotonin content. While the original formula contains floating wheat (a staple grain), the mechanistic principle established through this line of research suggests that cereals, including coarse grains with similar bioactive properties, may modulate the neuroimmune microenvironment through the gut-brain axis. Building upon this theoretical foundation, germination stress technology has been developed to process millet, leveraging physiological stress responses during germination to significantly enrich functional components. Through optimized soaking and germination conditions, the gamma-aminobutyric acid content in germinated millet can be substantially elevated. As the primary inhibitory neurotransmitter in the central nervous system, gut-derived gamma-aminobutyric acid can influence stress regulation and emotional stability *via* the gut-brain axis. This technology achieves a transformative upgrade from mechanistic elucidation to the development of novel food-based therapeutic raw materials.

3.3.2 Precision formulation design with dual-target modulation of mood and metabolism

Targeting the three typical conditions of premenstrual mood disorder, acute stress, and insomnia, this study designs a precision formula with dual "emotion and metabolism" targets, with the core objective of simultaneously intervening in the two major pathways of neurotransmitter synthesis and blood glucose fluctuation.

For premenstrual mood disorder, the formula focuses on the combination of magnesium-rich buckwheat and vitamin B6-rich wheat germ. Magnesium participates in the regulation of neuromuscular excitability, while vitamin B6, as a key coenzyme in the conversion of tryptophan to serotonin, exerts a direct effect on stabilizing premenstrual mood fluctuations. Evidence from randomized controlled trials indicates that magnesium and vitamin B6 supplementation can significantly reduce the total scores of premenstrual syndrome and improve mood-related symptoms. Buckwheat contains a lot of magnesium and is the type of low glycemic index cereals, and wheat germ is a natural high-quality source of B vitamins. Their synergy fulfills the two purposes of nutritional support as well as glycemic stabilization.

In acute stress scenarios, the design concept of the oat-based stress-reducing cereal bar is based on the regulatory process of low glycemic index carbohydrates on stress hormones. The high glycemic responses worsen the cortisol variations and the slow-release carbohydrates in oats give a constant supply of energy hence avoiding anxiety and irritability caused by the dramatic changes in blood glucose levels. In addition, the dietary fiber of

oats can have an indirect effect on the neuroimmune microenvironment *via* the gut-brain axis, providing a metabolic buffer to stress conditions.

The insomnia intervention formula is a combination of oats, *Ziziphus jujuba* seeds, and fermented cherry drink that covers the promotion of sleep and glycemic stability. As a traditional sedative component, *Ziziphus jujuba* seeds have been demonstrated by modern studies to regulate the activity of the GABAergic system. The fermented cherry drink has high natural melatonin precursors and the slow-release carbohydrate profile of oat helps to keep blood glucose levels stable throughout the night preventing awakenings due to nocturnal hypoglycemia. This formula combines the old dietary wisdom with the modern gut-brain axis processes to attain the synergistic optimization of sleep quality and metabolic health.

3.3.3 Establishment of a "psychobiotic prebiotic" screening platform

The main objective of creating a "psychobiotic prebiotic" screening platform is to screen and identify coarse grain fibers that can effectively activate specific psychobiotic strains to produce serotonin and GABA precursor compounds, thus building a functional raw material database for the development of functional foods for mood regulation. To fulfil this goal, it's important to overcome screening bottlenecks. The gut-on-a-chip system integrates high-throughput microfluidic chips with machine learning algorithms, enabling high-speed screening of functional performance of multiple candidate strains in standardized intestinal environments, as well as precise discrimination of subtle differences between bacterial strains in their therapeutic potential. This cutting-edge technology allows rapid screening of the best combinations from large combinatorial libraries of coarse grain fibers and probiotics. Moreover, screening approaches need to evolve from single fiber components to synergies of polysaccharide blends. Studies show that interactions between different source polysaccharides are more than simply additive. This offers practical advice for the development of psychobiotic prebiotics by showing that combinations are better than individual fibers. Once candidate polysaccharide combinations have been identified, fine-tuning is necessary. Prebiotics vary in their efficiency of carbon source utilization and metabolic patterns. Fine-tuning the levels of inulin, fructooligosaccharides and galactooligosaccharides greatly improves target psychobiotic growth rates and overall short-chain fatty acid production. This indicates that psychobiotic prebiotic libraries should not be a simple list of coarse grain fibers but rather consist of composite formulas that have undergone exhaustive proportional optimization and testing. The psychobiotic prebiotic screening platform moves from a conceptual framework to an engineering implementation by combining three aspects, namely the high throughput screening of gut-on-a-chip technology, the synergy enhancement strategy of polysaccharide combinations and the precision optimisation of prebiotic ratios, into a continuous technical process. This platform will allow coarse grain fibers to be systematically converted from generic dietary supplements into molecular tools for specific modulation of the gut microbiota's metabolic activities, offering essential raw material for converting nourishing the mind through food from descriptive terms into measurable, verifiable and standardised scientific approaches.

4 Industrial ecology and cultural reconstruction

4.1 Rethinking product logic

4.1.1 Industrial practice of function-oriented breeding

Function-oriented breeding (also known as trait-targeted or nutrition-driven breeding) is radically changing the coarse grain business model of an agricultural commodity based on yield to a competitive business model based on precision-functional nutrition. Unlike conventional breeding that focuses solely on high yield, stress resistance, and palatability, function-oriented breeding targets the enhanced biosynthesis of specific bioactive compounds, with each cultivar corresponding to a well-defined dietary health target. Coarse grains are no longer merely agricultural products but "plant bioreactors" that harness photosynthesis to produce FMH active substances.

Thick-aleurone breeding represents a significant practical direction of function-oriented breeding. Studies have introgressed the *ta1* aleurone-thickening trait through marker-assisted breeding, developing new lines with substantially thickened aleurone and markedly improved nutritional quality. The *ta1* mutant phenotype is caused by a point mutation, which redirects the cell fate of subaleurone cells from starchy endosperm to aleurone, doubling the number of aleurone cell layers and significantly increasing the contents of total proteins, lipids, dietary fibers, antioxidants, and vitamins.

Another typical case is the directional breeding of high- β -glucan *Qingke*. Comparative proteomic study of three highland barley cultivars with significantly different levels of β -glucan showed that differentially expressed proteins were mostly enriched in the pathways of β -glucan biosynthesis, carbohydrate metabolism and sugar degradation. It is noteworthy that several glycosidase and glycosyltransferase proteins were also strongly down-regulated in high- β -glucan cultivars decreasing the catabolism of polysaccharides and thus enhancing the accumulation of β -glucan. *In vitro* enzymatic inhibition assays have shown that β -glucan has relatively high inhibitory activity against α -glucosidase (with a maximum inhibition rate of 77%), but not lipase, which suggests that *Qingke* β -glucan can be used as a natural auxiliary hypoglycemic additive in functional foods.

Together, these examples demonstrate that the function-oriented breeding-driven transformation of the coarse grain industry essentially entails deliberate redesigning of crop metabolism using molecular breeding technologies, a radical metamorphosis of coarse grains as traditional agricultural commodities into FMH functional products.

4.1.2 High-value development of coarse grain proteins

Coarse grain-derived proteins are an important class of plant-derived functional proteins, mainly sourced from quinoa, millet, buckwheat, and other coarse grains. Emerging research has indicated that these proteins possess multiple physiological effects, including antioxidant, immunomodulatory, tumor chemopreventive and chemoprotective, anti-inflammatory, antihypertensive, antihyperglycemic, and antihyperlipidemic activities. The health-regulating effects of coarse grain proteins mainly stem from the bioactive short peptides produced by their degradation. These short peptides can either be naturally released through the endogenous digestive process in the human gastrointestinal tract or be directionally prepared *via* processing

technologies such as enzymatic hydrolysis, microbial fermentation, and *in vitro* simulated digestion. Furthermore, compared with animal-derived proteins, some coarse grain proteins have a lower digestibility due to their dense structure. The undigested components of coarse grain proteins in the host's gastrointestinal tract can enter the colon and be metabolized and transformed by the gut microbiota as fermentation substrates, generating physiologically active microbiota metabolites such as short-chain fatty acids. These metabolites can form a synergistic effect with the aforementioned bioactive short peptides and jointly participate in the regulation of the body's physiological functions and the maintenance of health.

4.1.3 Postbiotic-oriented formulation design paradigm

The traditional approach to developing probiotics focuses on "supplementing the host with specific live bacteria", while the emerging postbiotic-oriented formula design represents a paradigm shift. The ultimate goal of development now focuses on "into what can this formulation be transformed by the host microbiota?" Live bacteria carry safety risks such as strains off-target, conditionally pathogenic risks, and the spread of antibiotic resistance genes. The health effects of probiotics are mediated by their metabolic products, namely, postbiotics. Postbiotics, being non-living preparations of microbes and their components, avoid these risks while still being able to regulate immunity, repair barriers, and improve metabolism through various active substances such as short-chain fatty acids (SCFAs), bacteriocins, extracellular polysaccharides, and neuroactive molecules. The design of formulations is shifting from "strain selection" to precise regulation of the "substrate, microbiota, metabolite" relationship. The production of GABA, a key mediator in the gut-brain axis, heavily depends on specific gut bacteria that carry the glutamate decarboxylase (GAD) gene, such as *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*. Dietary substrates, glutamate/glutamine, microenvironmental pH, and cofactors such as pyridoxal phosphate directly affect the expression efficiency and yield of the GAD system. Dietary fiber is fermented by butyrate-producing bacteria such as *Faecalibacterium prausnitzii* and *Eubacterium rectale* into SCFAs (acetate, propionate, and butyrate). These not only supply energy to colon cells but also contribute to the maintenance of gut barrier integrity and control of local and systemic immune responses through the activation of free fatty acid receptors (FFAR2/FFAR3) and inhibition of histone deacetylases (HDACs). It is based on this that the new generation of postbiotic-oriented formulas can be used to treat the host microbiota as a programmable endogenous bioreactor, with the formula being the programming language which instructs this bioreactor to synthesize target functional molecules. With the development of metabolomics and AI-based microbiota-metabolite correlation prediction models, it is now possible to design precision formula that is microbiota-responsive based on the baseline microbiota profile of an individual, which opens up new avenues in standardizing, personalizing, and clinically using postbiotic preparations in metabolic and neuropsychiatric disorders.

4.2 Business models and the professional ecosystem

4.2.1 "Food as medicine as a service" as a subscription model for health improvement

The essence of the change in the food as medicine as a service

(FMaaS) model is that the exchange value in the coarse grain industry will shift to the product and focus on the health outcomes that consumers want. This requires users to pay not by a unit of coarse grains, but by continuous metabolic improvement. Whether this change is viable depends on the combination of two technological trends. The first one is the integration of wearable devices with digital health platforms without any problems. Existing technologies have the potential to provide personalized lifestyle intervention recommendations through continuous monitoring of physiological measures like blood glucose and heart rate variability, combined with behavioral data, resulting in significant changes in hyperglycemia, glycemic variability, and indicators of metabolic syndrome. The second trend is the real-time decision-making ability powered by AI, where deep learning algorithms can analyze multimodal sensor data to identify early indicators of metabolic abnormalities and trigger specific dietary adjustments in advance. Here, the function of coarse grains is completely transformed. They transform from commodities to health intervention agents. Their structures and processing conditions can be tailored in real-time according to individual metabolic needs to enhance their prebiotic activities from dietary fibre, anti-inflammatory activities of polyphenolic compounds and metabolic regulating activities of other phytochemicals. The success of this model relies not only on technological innovation but also consumer acceptance of using wearable systems for health management. Consumer interest in devices with health monitoring functions far exceeds that of devices with daily assistance functions. This indicates a market cognitive basis is being established around "paying for continuous health improvement". With products, data and health outcomes in a closed-loop subscription system, the value logic of the coarse grain industry will be transformed. It will shift from "tonnage sales" to "service sales". At the same time, coarse grains themselves will evolve from sidekicks on dinner tables to become key instruments for personalised metabolic management.

FMaaS conceptually is an attractive model, but has significant barriers to adoption due to conflicting stakeholder interests. The conventional agricultural producers are also enjoying the advantages of volume-based commodity selling and might not want to shift to outcome-based systems that demand investment in traceability, data infrastructure, and functional product development. Food processing industry is challenged with reformulating products to fit precision nutrition requirements without compromising on taste and affordability. Data analytics and AI-driven personalization are areas of great opportunities to technology enterprises, yet their interests might not align with those of healthcare providers who have clinical responsibility of dietary advice. Policymakers need to weigh the preventive nutrition benefits to the population against the regulatory challenges of authorizing food-as-medicine claims and reimbursement channels. To transform the FMaaS concept into a vision into practice, the creation of win-win mechanisms, including public-private partnerships sharing the costs and benefits of infrastructure investment, phased regulatory sandboxes enabling controlled experimentation, and outcomes-based reimbursement models aligning incentives among stakeholders will be critical.

4.2.2 The rise of the gut ecosystem architect

In addition to the profound incorporation of the FMH concept and microecological interventions, a new, multidisciplinary paradigm based on the idea of gut ecological design is gaining

momentum at an unprecedented rate. The essence of this paradigm is to develop specific dietary intervention schemes based on the synergistic combinations of coarse grains, FMH materials, and probiotics/prebiotics to target-restructure the gut microecological framework and enable self-reconstruction of the microbiota. In particular, resistant starch, β -glucan, and polyphenols are found in high concentrations in coarse grains (including oats, buckwheat, and sorghum). These bioactive ingredients are fermentable substrates that greatly increase the synthesis of short-chain fatty acids (SCFAs), thus strengthening the integrity of the gut barrier. In the meantime, FMH materials possess both characteristics of nutritional support and immunomodulation. Their characteristic polysaccharides, when fermentatively biotransformed by specific beneficial taxa (for example, *Lactobacillus* and *Bifidobacterium*), not only display dramatically enhanced bioavailability but also generate fermentates that act synergistically with the probiotics to exert robust anti-inflammatory and metabolic regulatory effects. Since the inter-individual variability of the baseline microbiota is one of the main bottlenecks of variable efficacy, future gut ecological design should be closely intertwined with nutritional science (dietary patterns and macronutrient ratios), microbiology (microbiota structure and functional metagenomic profiles) and herbal pharmacology (meridian tropism and active constituents). This integration will develop a three-part substrate-microbiota-host interaction model, which will produce customizable, predictable, and evaluable personalized microecological intervention strategies.

4.2.3 Chronic disease management center

The guiding principle of the chronic disease management center is to establish precision dietary intervention as a major therapeutic approach to chronic metabolic conditions, and not just an adjunct to pharmacotherapy. This scientific hypothesis has been given some initial confirmation by several recent clinical trials. In a randomized controlled trial of patients with metabolic syndrome, interventions based on Mediterranean diet, which emphasized coarse grains, plant proteins, and healthy fats, were able to improve metabolic parameters significantly in six months and partially reverse metabolic syndrome, thereby offering direct clinical support to non-pharmacological food-as-medicine interventions. At the same time, the effectiveness of individualized dietary interventions in treating chronic diseases has also been confirmed in particular disease settings. One case report on chronic gastroesophageal reflux disease concluded that considerable and long-term symptomatic relief was achieved following determination of personal dietary trigger factors and subsequent specific dietary changes, which in turn decreased long-term use of acid-suppressing drugs. Together, these results indicate that as dietary interventions change their focus to precision dietary intervention protocols based on individual phenotypic and metabolic profiles, their impact changes to be more palliative than substantive management. It is on this understanding that the operational mechanism of the chronic disease management center must go beyond empirical practice by putting in place a closed-loop validation system that is data-driven. This system would combine real-world data (RWD) with longitudinal clinical measures to track the changes in metabolic patterns under precision dietary interventions continuously, and generate quantifiable health improvement data that dynamically confirms the effectiveness of nutritional interventions. Beyond providing patients with chronic diseases with verifiable

non-pharmacological management options, the importance of this model goes beyond that. More importantly, it raises the clinical worth of dietary therapy as an adjunctive regulation to a strategic level of independent intervention. This change builds up all the evidence-based bases needed to incorporate nutritional prescriptions into mainstream medical systems.

4.3 Standard development and the policy ecosystem

4.3.1 Product standards and grading for functional coarse grains

The essence of standardizing functional coarse grains is not to make claims like high fiber or high protein marketing terms, but to base every health claim on quantifiable, traceable and gradable bioactive ingredients. It is recommended that a three-tier system be used. First, check the botanical variety and source of the ingredient. Second, establish minimum effective levels and test procedures of β -glucan, resistant starch, anthocyanins and phenolics. Third, relate intake advice with use cases, target populations and compatibility limits. Recent research indicates that oat and barley products have to make their health claims regarding β -glucan dose and product form, whereas there is also clear evidence of metabolic and antioxidant activities of resistant starch and sorghum phenolics. Thus, the grading should be based not on what has been added in the product but how much is delivered, how much is retained and to whom it works, with the inclusion of concepts of FMH, such as nature, meridian tropism and dietary cautions.

4.3.2 Promoting food-based dietary prescriptions into clinical practice and insurance

Institutionalizing the FMH value of coarse grains is an important step in incorporating food-based nutritional prescriptions into clinical practice and health insurance systems. The burden of chronic diseases associated with diet has become a global priority. In the U.S. alone, nutrition-related disease results in more than 600,000 deaths and \$1.1 trillion in healthcare costs and lost productivity each year. In this context, the "Food is Medicine" movement is transforming global health care. Global examples, such as the "Food is Medicine" programs in the United States, offer lessons learned. The Centers for Medicare and Medicaid Services (CMS) in the United States has started to consider dietary interventions *via* Medicaid waivers, and bills like the National Food as Medicine Program Act have been proposed in Congress. According to national surveys, more than two-thirds of respondents agree that Food is Medicine programs should be covered by Medicare and Medicaid. Although these developments do not directly prove the possibility of reimbursement within the Chinese healthcare system, they provide some useful insights into how to implement them, how to evaluate them, and what can go wrong.

In terms of TCM, the philosophy behind food-based prescriptions is that of pattern-based dietary therapy, which controls *zang-fu* organs based on the properties, flavors and channel entries of coarse grains. Sweet and neutral oats are introduced into the spleen and stomach channels, tonifying *qi* and reinforcing the spleen. Sweet, bland and slightly cold *Coix* seed enters the channels of the spleen, stomach and lung, strengthening the spleen and removing dampness. Their compatibility deals with metabolic disorders of the spleen-deficiency type with dampness. The fact that health insurance covers food-based prescriptions essentially recognizes that dietary therapy is therapy. Based on global experience, China can implement staple food prescriptions

in primary care chronic disease management, integrate qualified coarse grain formulations into outpatient pooled payment, demonstrate their cost-effectiveness using real-world data and bring the concept of food-based therapy out of folk wisdom to an institutionalized approach to preventing and treating chronic diseases.

There are significant policy, regulatory and implementation challenges to translating food-based dietary prescriptions into clinical practice and insurance reimbursement. The key issue is the absence of standardised evidence requirements for "prescribable" food-based interventions. Food-based interventions do not have a similar pathway to approval as pharmaceutical drugs, which undergo extensive clinical trials. Second, food products are diverse (due to differences in cultivation, processing and storage), making it difficult to standardize and control quality. Third, implementing dietary prescriptions in clinical practice involves educating clinicians, adapting electronic health records, and creating new payment models. We recommend that the most promising approach in the short term is to prioritise a small number of well-defined coarse grain formulations with robust mechanistic and clinical data, and to establish pilot programs that provide the real-world evidence to guide policy decisions.

4.4 Contemporary narrative of dietary therapy culture

4.4.1 Contemporary reconstruction of the classical dietary therapy lineage

The systematic collection of the coarse grain dietary therapy formulas in ancient literature like *Shi Liao Ben Cao* (*Dietetic Materia Medica*) and putting them through scientific validation is the essence of the modern day reconstruction of classical food-based therapy. *Shi Liao Ben Cao* by Xian Meng, a writer of the Tang Dynasty, was the first monograph on dietary therapy in the world. It formulated the theory of FMH, recorded the difference between diet in northern and southern China, and systematically explained the properties, actions and contraindications of foods according to their categories, thus forming the theoretical basis of dietary therapy. The book discusses the healing qualities and uses of more than 200 food ingredients, such as coarse grains, vegetables, and fruits. Its doctrine of equal stress upon prevention and treatment, moderation in everything, and adaptation of consumption to the person, season, and locality are highly educative.

The main approach to modern reconstruction is based on a three-step plan: Ancient formula screening, mechanistic validation, product translation. Consider an example of the Gan Mai Dazao Tang (Licorice-Wheat-Jujube Decoction). This formula, which is based on *Zhongjing Zhang Jin Gui Yao Lue* (*Essentials of the Golden Cabinet*), consists of licorice, wheat and jujube, with wheat (sweet and cool, entering the heart channel) nourishing the heart and liver, calming the spirit, and alleviating restlessness. Recent studies have converted this formula into anti-anxiety FMH products and are investigating its mechanisms using the gut-brain axis. Based on this, it is possible to create a solar term coarse grain box that would convert the time-based medical philosophy of dispersing the liver in spring, clearing the heart in summer, moistening the lung in autumn, and tonifying the kidney in winter into seasonal products that can be consumed. Buckwheat (cool, entering the liver channel) may be used in spring together with FMH materials to clear the liver and brighten the eyes. During summer, FMH materials can be mixed with coarse grains to purge the heart, subdue the spirit, feed *Yin* and

moisten dryness. During autumn, it is possible to combine oats (sweet and neutral, entering the spleen and stomach channels) with FMH materials to moisten the lung and suppress cough. Coarse grains may be used in winter to mix with FMH materials to tonify the kidney and replenish essence. This translation not only gives ancient formulas a modern scientific meaning but also brings dietary culture back into everyday life in product forms that are compatible with the modern lifestyles, not by educating the youth on how to cook porridge, but by incorporating traditional wisdom into ready-to-eat grain bars, fashionable drinks, and other contemporary consumer goods, attaining the living transmission of cultural heritage.

4.4.2 Branded development of regional dietary wisdom

The essence of the branded development of regional dietary wisdom is the integration of the principle of localization into the coarse grain food-based therapy product system and empowering genuine regional dietary brands with geographical indications (GIs). The large size of China leads to the fact that different waters and soils bring up different peoples. Different regions have developed unique traditions of dietary therapy due to the climatic conditions and eating habits. *Shi Liao Ben Cao* already observed the difference in diet between northern and southern China. Underlying these variations is the literal expression of the doctrine of TCM, which is the treatment based on the person, season, and place.

Currently, GI certification provides an institutional foundation for the branding of regional dietary therapy. Qinzhou Yellow Millet, a nationally recognized GI product, is renowned as "imperial tribute millet" and is credited with clearing heat, promoting diuresis, reducing edema, and nourishing *Yin*. Xingxian millet has been included in the National GI Product Protection List. GI products such as Baicheng oats have formed a regional brand matrix.

Building on these GI products, "regional dietary formulas" can be further developed. In the northwest, where the climate is dry, buckwheat and oats can be combined with lily and apricot kernel to create a "moisture-clearing formula". Buckwheat, cool and entering the liver channel, clears the liver, while lily, sweet and cold, entering the lung channel, moistens the lung. In the southwest, where it is humid and rainy, *Coix* seed can be combined with tangerine peel to create a "dampness-eliminating formula". *Coix* seed fortifies the spleen and eliminates dampness, and tangerine peel rectifies *qi* and transforms dampness, jointly regulating the Triple Burner. In the northeast, with its cold frozen soil, millet can be combined with longan and red dates to create a "warming-tonifying formula". Millet, entering the kidney channel, warms and tonifies kidney Yang. Longan, entering the heart and spleen channels, tonifies the heart and spleen. Red dates, entering the spleen and stomach channels, tonify the middle and augment *qi*, warming without drying. In the Jiangnan region, where plum rains linger, *Coix* seed can be combined with lotus leaf to create a "plum rain package". *Coix* seed promotes diuresis and reduces edema, and lotus leaf raises the clear and lowers the turbid, combining clearing and draining actions.

The empowerment of authentic regional dietary brands with GIs is, in a way, the ecological nexus of terroir, crop, human body turned into familiar and reliable consumer symbols, such that when a consumer picks up a bag of coarse grains, he or she is not only picking up a food, but the health wisdom of a particular land and its people.

5 Key technological breakthroughs

5.1 Technological breakthroughs in raw materials

5.1.1 Enzymatic hydrolysis and molecular reassembly of coarse grain proteins

Proteins of buckwheat and quinoa have received a growing interest as sustainable plant-based sources of bioactive peptides that hold great potential in promoting health. Both common buckwheat (*Fagopyrum esculentum*) and tartary buckwheat (*F. tataricum*) have good amino acid profiles, whereas quinoa (*Chenopodium quinoa*) is appreciated due to its high nutritional quality, digestibility, and gluten-free nature.

Buckwheat peptides with dipeptidyl peptidase-4 (DPP-4) inhibitory activity, including Ile-Pro-Leu and Ile-Pro-Trp, are obtained by enzymatic hydrolysis with Alcalase and Flavourzyme. The latter is reported for the first time as an effective food-derived DPP-4 inhibitor, while both peptides show significant activity, highlighting buckwheat proteins as a source of bioactive compounds regulating blood glucose levels. Feeding a peptide-enriched fraction of buckwheat to rats resulted in small but significant decreases in postprandial blood glucose levels, indicating potential benefits for glycemic control. Moreover, a low-molecular-weight glutaredoxin (rbGrx) purified from buckwheat exhibits life-extending properties in *Caenorhabditis elegans* under both normal and stress conditions. This is believed to be due to direct scavenging of reactive oxygen species (ROS) and indirect antioxidant effects through induction of the stress-inducible transcription factor hsf-1. These results suggest that rbGrx may be used to improve healthy aging and prevent age-related diseases in humans by increasing stress resistance.

Quinoa protein hydrolysates, especially those produced using Alcalase, have high levels of hydrolysis, nitrogen recovery and antioxidant activity. *In vitro* digestion experiments show that quinoa peptides are resistant to gastric digestion but are digested in the small intestine, with a high level of antioxidant activity after gastrointestinal transit. Moreover, preclinical studies suggest that quinoa peptides are context-dependent regulators of gut microbiome, making quinoa an attractive target for targeted gut health strategies. Alkaline protease followed by trypsin sequential hydrolysis enhances the degree of hydrolysis and antioxidant capacity of quinoa proteins. Of the peptides identified, GPGGGGKGEMF (GF-11) exhibits the highest binding affinity in molecular docking simulations and is effective in promoting cellular redox homeostasis through decreasing reactive oxygen species and malondialdehyde content, increasing antioxidant enzyme activities and activating the Keap1-Nrf2 pathway.

Taken together, these studies highlight the use of buckwheat and quinoa proteins as functional food ingredients. Their peptides demonstrate multifunctional bioactivities such as modulation of gut microbiome, glycemic regulation, resistance to oxidative stress and maintenance of metabolic health, thus providing a scientific rationale for the development of plant-based nutraceuticals and functional foods.

5.1.2 Key transformation mechanisms in fermentation

Multigrain fermentation alters the macromolecules in cereal matrices by microbial metabolism and enzymatic reactions, which enhances the nutritional, textural and functional characteristics of the products. This change goes all the way through the chain of raw material pretreatment to final product.

Efficient transformation requires biological or physical pretreatments prior to fermentation. Multigrain raw materials are subjected to malting, roasting and germination. As an example, pearl millet can be malted, barley and quinoa roasted, which partially breaks down polysaccharides and alters starch to give more accessible substrates to further processing and possible fermentation. Similarly, the germination of quinoa changes the chemical composition of the flour to a great extent, providing the opportunity to convert the nutrients further.

The major fermentation phase is characterized by the breakdown of the major grain constituents as the key transformation. Microbial or exogenous enzymes are used to disintegrate starch and non-starch polysaccharides (NSP). In seera, a traditional Indian food that is fermented using a combination of sorghum and finger millet, starch granules are broken, deformed and cracked, which means that there is surface erosion and structural weakening due to fermentation. The effectiveness of enzymatic conversion was supported in a broiler model where addition of NSP-degrading enzymes to a barley-based multigrain diet and extension of crop retention by intermittent feeding enhanced early interaction between the enzymes and their substrates and decreased intestinal digesta viscosity, on a digestive physiology basis.

Beyond carbohydrate degradation, the transformation of proteins and phenolic compounds is also important. During *in vitro* digestion of multigrain noodles, the addition of various soluble dietary fibers markedly increased the degree of protein hydrolysis, pointing to a positive link between fiber-associated changes during fermentation and protein digestion. At the same time, the release of polyphenols and the enhancement of antioxidant activity are additional key transformation features. Fermenting multigrain blends with sourdough, or integrating fermentation with three-dimensional (3D) printing, has been shown to raise total flavonoid and phenolic contents and to improve antioxidant activity, likely because fermentation releases bound phenolics from cell-wall matrices. Improvements in amino acid profiles, including elevated methionine, aspartic acid and glutamic acid, as well as higher levels of minerals such as iron and phosphorus further support the role of fermentation in enhancing nutrient density.

These matrix-level changes translate into altered physiological responses. Animal experiments show that rats fed multigrain breads fermented with different sourdoughs exhibit reduced postprandial blood glucose and insulin, and modulated blood triacylglycerols and the inflammatory marker MCP-1. These effects are starter-specific and closely linked to differences in sugars, organic acids and microbial composition among sourdoughs, revealing that distinct fermentation systems drive divergent metabolic conversion pathways. Regulation of FODMAPs (lowering fermentable oligo-, di- and monosaccharides and polyols through fermentation) is another mechanism by which multigrain fermentation improves digestive tolerance.

5.1.3 Synergistic fermentation of polysaccharide combinations

Multigrain systems contain structurally diverse polysaccharides, including arabinoxylans, β -glucans, fructans, resistant starch and oligosaccharides. During fermentation, these polysaccharides do not function independently. Instead, they interact synergistically with microbial communities, exogenous enzymes and processing methods, collectively shaping the quality and functionality of the final product.

Microorganisms and different types of polysaccharides engage in synergistic metabolism. Soluble dietary fibers from different sources, such as fructo-oligosaccharides, galacto-oligosaccharides and high-amylose corn starch, acted together during *in vitro* fermentation of multigrain noodles. They lowered the pH of the fermentation system, significantly boosted short-chain fatty acid production and increased the relative abundance of *Bifidobacterium*, *Lactobacillus* and *Clostridium_sensu_stricto_1* at the genus level. Such positive modulation of gut microecology through multiple fibers represents a synergistic benefit that a single fiber cannot achieve.

Exogenous enzymes and endogenous substrates also act synergistically. Multigrain NSP are structurally complex and are not efficiently hydrolyzed by a single enzyme. In broiler studies, the commercial multi-enzyme preparation used contained several NSP-degrading activities. These enzymes worked together on the mixed polysaccharides of grains such as barley and, during prolonged digesta retention, synergistically increased volatile fatty acid concentrations in the digesta while reducing starch and moisture in the ileum, reflecting effective cooperation within the enzyme system and between enzymes and substrates.

The fermentation of the same multigrain matrix by different microbial consortia produces distinct metabolic imprints. Using three sourdoughs (Rebola, Carla and San Francisco) to ferment the identical multigrain bread yielded clearly different physiological responses in rats. SF sourdough bread performed best in improving the relative apparent absorption of minerals, whereas Ca sourdough bread specifically lowered blood lipids. The interaction between multi-strain starters and the complex multigrain substrate thus generates metabolites with differing sugar, organic acid and bioactive peptide profiles, leading to differentiated health effects.

Combining processing methods with biological fermentation is further extending the application of multigrain polysaccharides. The combination of sourdough fermentation and quinoa germination with 3D food printing resulted in biscuits that retained high levels of fiber and protein but exhibited differences in appearance, amino acid profile and antioxidant activity due to the processing technique, showing the synergy between biological transformation and physical shaping. Likewise, even in the absence of fermentation, it is possible to control precisely the water absorption index, solubility and microstructure of multigrain beverage premixes by combining polysaccharide pre-degradation steps like malting and roasting with extrusion, offering a means to produce instant multigrain products without further fermentation.

However, market surveys show that claims of fermentation on commercial bread products are rapidly increasing and often come with non-traditional ingredients, and can generate an unjustified "health halo". So, it's important to clarify the mechanisms of synergistic fermentation of multigrain polysaccharides to separate fact from fiction and provide a scientific foundation for their health benefits. The next step is to unravel the interactions between targeted polysaccharide combinations and specific microbial populations to guide the design and functional engineering of multigrain fermented foods.

5.2 Technological breakthroughs in processing

5.2.1 Texture optimization and bitterness reduction with taste masking

Coarse grains with dual medicinal and edible values are blessed

with high nutritional properties and physiological bioactivities. Nevertheless, natural components of these coarse grains have a very bitter taste, which adversely affects the acceptability of products, their profound processing and industrialization. For example, rutin found in tartary buckwheat, and saponins present in quinoa. Conventional standalone debittering approaches such as soaking, high-temperature rinsing and resin adsorption deliver unsatisfactory debittering outcomes and trigger massive loss of active components such as rutin and saponins, failing to balance flavor improvement and nutrient retention simultaneously.

Individual debittering technologies have obvious drawbacks. Enzymatic hydrolysis can only degrade small-molecule bitter compounds *via* exopeptidases yet fails to restructure hard-to-decompose limonin and saponins. Microbial fermentation transforms partial bitter components independently but suffers from lengthy fermentation cycles and unstable flavor profiles. Microcapsule embedding merely masks bitterness physically rather than fundamentally modifying the structure of bitter substances. Studies have investigated the improvement effect of cyclodextrins through complexation on bitterness. The results of sensory evaluation and electronic tongue analysis indicated that when cyclodextrins were added at a mass ratio of 1:1, the bitterness of the solution could be reduced by forming complexes. Compared with α -cyclodextrin and γ -cyclodextrin, β -cyclodextrin has a better bitterness masking effect.

The coupled three-in-one system of embedding, enzymatic hydrolysis and fermentation realizes synergistic effects through biodegradation, structural modification and physical masking, standing out as an optimal solution to the bitterness issue of coarse grains.

Procedurally, compound enzymatic hydrolysis firstly cleaves macromolecular structures of saponins and limonin to destroy binding sites for bitter receptors. Subsequent fermentation by lactic acid bacteria and yeast further decomposes residual bitter substances and produces flavor metabolites to optimize the inherent taste of cereals. Finally, microcapsule embedding with polysaccharide wall materials isolates trace remaining bitter ingredients from taste buds. Meanwhile, this technique prevents oxidative degradation of bioactive substances such as rutin during processing and storage. Studies have shown that the perception intensity of bitterness and sourness in foods with foam or emulsion structure decreased, while the perception of sweetness was stronger.

At present, the combined three-in-one process still faces practical challenges including difficult parameter optimization, lack of universal standards applicable to diverse raw materials and high production costs. Future research shall formulate customized technological parameters targeting tartary buckwheat and quinoa, streamline manufacturing procedures and cut production costs. These efforts will promote large-scale popularization of this debittering technology and advance the industrialization of functional foods derived from medicinal and edible coarse grains.

It is noteworthy that bitterness masking and texture optimization, as technically oriented, play an essential strategic role. The basic requirement of coarse grains to be maintained as daily intervention vehicles is sensory acceptability. Regardless of the strength of the health evidence, consumers will not follow interventions that are not tasty or have bad mouthfeel. This fact puts formulation science in the focal point of the translational process of mechanistic evidence to real-world impact. The future studies need to focus on the creation of standardized protocols of sensory evaluation and determination of processing parameters

that maximize palatability and bioactivity retention.

5.2.2 Preservation technologies for fresh-ready coarse grain foods

The major issue with fresh-ready coarse grain foods is that starch-based matrices readily lose water, retrograde and harden on chilled storage and reheating, and fresh wet products are also susceptible to mold and aerobic microbial contamination. A formulation-to-control-retrogradation-packaging-to-control-oxygen-and-water-level-rehydration-to-reconstruct-structure strategy should be given priority. Natural anti-staling compounds like inulin and soluble dietary fibers may interfere with the rearrangement of amylose and amylopectin at the formulation end. Modified atmosphere packaging can help to minimize oxygen contact during distribution, stabilize water activity and slow down quality degradation. In the case of convenience products, freeze-drying may be used to form porous networks which allow rice noodles, buckwheat noodles and highland barley cakes to regain elasticity and grain flavor upon rehydration. Recent studies on fresh rice noodle retrogradation, fresh noodle modified atmosphere packaging, and freeze-dried rice noodle rehydration justify this combined method to enhance texture, microbial safety, and edible quality. To scale up, hardness rebound, rehydration time, sensory retention and shelf life should be evaluated to make sure that freshness-preservation technologies enable the manufacture of fresh, low-additive, and distributable coarse grain products based on both food and medicinal ingredients in the FMH model.

5.2.3 Colonic targeted delivery of active ingredients

The role of gut microbiota in regulating the metabolic health of the host has been well established. But can dietary bioactive compounds, such as resistant starch, polyphenols, short-chain fatty acid precursors and microbial metabolites reach the colon undamaged and be specifically used by target bacteria is the key bottleneck that dictates their effectiveness. Digestive enzymes, bile salts and gastric acid present a daunting barrier to most active ingredients being degraded or absorbed before they get to the colon with very low bioavailability. Hence, the creation of efficient anti-digestive encapsulation systems in the coarse grain processing to deliver colonic targeted delivery is a frontier issue in food processing technology.

Starch, due to its natural resistance to digestion and outstanding biocompatibility is one of the most promising carrier materials to be used in colonic delivery. Covalent grafting of active compounds onto starch molecules has allowed researchers to ensure that these components are not degraded during the passage through the stomach and small intestine but are released only after enzymatic cleavage by the microbiota in the colon. Research has esterified indole-3-acetic acid (IAA), a metabolite of gut microbes, onto waxy maize starch, normal maize starch, and high-amylose maize starch, comparing systematically the effects of various amylose contents on the efficiency of colonic delivery. The success of grafting of IAA onto the starch backbone was confirmed by ¹H NMR and FT-IR. The results of *in vitro* digestion revealed that the resistant starch content of all three esterified starches increased significantly to 66%–68%. The high-amylose maize starch-IAA ester was found to have the highest concentration of IAA in the colon (4.19 mmol/kg) compared to the stomach and small intestine, which proved the protective effect of starch carrier on colonic delivery of IAA. 16S rRNA sequencing further demonstrated that all three indole-acetylated starches reduced the Firmicutes-to-Bacteroidetes ratio and enriched beneficial short-

chain fatty acid-producing genera such as *Oscillospira* and *Parabacteroides*. Among them, the normal maize starch-IAA ester group showed the highest microbial richness and significantly alleviated DSS-induced colitis symptoms. This study provides direct experimental evidence for achieving precise colonic delivery of active compounds through starch covalent modification.

At the physical encapsulation level, scientists have exploited layer-by-layer assembly of polyelectrolyte polysaccharides to form dense gel networks which surround active ingredients and provide a physical barrier to attack by digestive enzymes. Research has produced polyelectrolyte complex (PEC) microparticles with sodium alginate (SA), gellan gum (GG), and chitosan (CS). FT-IR analysis confirmed the formation of stable ionic bonds between the protonated amine groups ($-NH_3^+$) of chitosan and the negatively charged carboxylate groups ($-COO^-$) of sodium alginate and gellan gum, constructing a highly hydrophilic hydrogel network. This structure withstood heat treatment and simulated digestive fluids, demonstrating excellent stability. The rate of release of lauric acid during *in vitro* simulated digestion of the PEC-microencapsulated complex was consistently low at 5%–6%. XRD analysis showed that the V-type crystalline structure of starch was preserved after encapsulation, and even after intestinal digestion, strong diffraction peaks remained, giving a crystallographic explanation to its resistance to enzymatic breakdown. After PEC encapsulation, high levels of slowly digestible starch (SDS) and resistant starch (RS) contents were maintained at high values greater than 50% and 30% respectively with low release of lauric acid validating the possibility of multilayer polysaccharide encapsulation to deliver to the colon. Other studies have developed sodium alginate/carboxymethyl chitosan microcapsules, further corroborating the physical barrier effect of dense gel networks. As sodium alginate concentration increased from 0.5% to 2%, the swelling degree of microcapsules at 95 °C decreased from 15.28 g/g to 3.76 g/g, while resistant starch content increased from 42.37% to 57.65%. This study reveals a core principle: Precise regulation of wall material concentration directly dictates the compactness of the encapsulation system, which in turn determines the integrity rate of active ingredients reaching the colon.

The layered cellular structure of natural cereal endosperm has inspired researchers to investigate biomimetic encapsulation systems which allow the staged release of active ingredients in the digestive tract. Research has developed oat-based biomimetic macrocapsules with core-shell structures using ionic crosslinking (alginate- Ca^{2+} coordination), polyelectrolyte complexation (chitosan-TTPP) and their combination, co-encapsulating oat starch and protein into a nutrient-dense core. The chitosan/calcium alginate bilayer (SC-3) showed the highest performance: Shell thickness of about 20.1 μm , cooked springiness of 0.97 and resistant starch content 3.96 times (raw) and 4.34 times (cooked) that of native oat starch.

In vitro digestion structural evolution analysis showed a layered response mechanism. The protein-reinforced starch core was still partially intact at 120 min, whereas the outer shell of SC-3 started to disintegrate at 60 min. This stratified protection model (sacrificial outer layer, resilient inner core) greatly decreased the rate of starch digestion and significantly enhanced the percentages of slowly digestible and resistant starch.

Anti-digestive encapsulation systems are further enhanced by the introduction of proteins that provide another level of structural control. Research has used transglutaminase (TG) and proanthocyanidin (PC) to synergistically crosslink proteins,

which were then complexed with corn starch. TG catalyzed the ϵ -(γ -glutamyl)-lysine isopeptide bonds between protein molecules, and PC also created covalent crosslinks creating a denser protein network. This network surrounded starch granules, both as a physical barrier to amylase access, and hydrogen bonding and electrostatic interactions with starch during co-gelatinization. Structural analysis showed that the synergistic effect of TG and PC reduced the content of α -helix and increased the content of β -sheet, facilitating orderly protein aggregation and network strengthening, thus reducing significantly the content of rapidly digestible starch and increasing the content of slowly digestible and resistant starch fractions.

Since covalent grafting onto starch, multilayer polysaccharide physical barriers, and biomimetic core-shell layered release, to protein crosslinking network reinforcement, anti-digestive encapsulation technologies are moving towards the concept of single physical protection to multi-level precision regulation. The overall understanding of these studies is that effective colonic targeted delivery does not merely entail wrapping active ingredients but involves a rational design of carrier structure, composition and response kinetics based on the unique physiological conditions of various parts of the digestive tract (gastric acid, enzymatic hydrolysis, pH and microbial distribution). For coarse grain processing, this means that naturally occurring active components, such as sorghum resistant dextrins, oat β -glucans, and various polyphenols, can be transformed from "co-digested with meals" to "precisely delivered to the colon" through the above encapsulation strategies. The future technological frontier in coarse grain deep processing should be guided by the "structure design, targeted release, microbiota response" paradigm, converting bioactive compounds in coarse grains into potential modulators of gut ecology.

5.2.4 3D printing of dietary therapy micro-pellets

3D food printing provides a breakthrough digital manufacturing approach for the engineering implementation of the above-mentioned microbiota-targeted interventions based on homology of medicine and food. This technology enables the direct use of coarse grain flours, which are rich in complex carbohydrates, as natural network-forming scaffolds, and their one-step co-printing with viable probiotic strains to fabricate structurally defined health-oriented micro-pellets with high precision. Studies have encapsulated *Bifidobacterium bifidum* in starch-based matrices with a pH-sensitive alginate/pectin shell using 3D printing, achieving a high survival rate of 96%. After incubation in simulated gastric fluid at pH 1.2 for 2 h, the survival rate remained as high as 83.1%, whereas the non-encapsulated control showed almost complete loss of viability. In simulated intestinal fluid at pH 6.8, both the uncoated and coated cells maintained high viability, at 93.2% and 92.0%, respectively.

The digital nature of 3D printing further allows researchers to finely tune the internal porosity, infill density, and geometric architecture of the micro-pellets, such as hollow, porous, or honeycomb-like structures, thereby precisely modulating their dissolution kinetics and enzymatic degradation behavior in *in vitro* digestion and texture analysis models. This engineering approach allows two levels of control. For instance, on the one hand, structural design can slow down starch digestion and gastric emptying when combined with coarse grain matrices high in dietary fiber and resistant starch, resulting in a more gradual glucose release postprandially. On the other hand, multilayer or core-shell structures, combined with pH-responsive materials, can

be used to program the release kinetics of bioactive food compounds and probiotics, thereby achieving more targeted spatiotemporal co-delivery in specific gut regions such as the distal colon. This transition from ingredient-based formulation to structure-based delivery is driving personalised, data-driven microbiota-directed nutrition from an idea to an engineerable technology.

5.3 Technological breakthroughs in data

5.3.1 Real-time feedback closed-loop system integrating CGM and wearable devices

The fundamental engineering challenge of a real-time feedback closed-loop system that is coupled with CGM and wearable devices is to convert coarse-grain dietary regimens based on predefined, fixed formulae into autonomous control systems capable of responding to the real-time physiological state of an individual. The real-time glycemic fluctuation information given by CGM not only forms the very basis of the signal of glycemic management but also presents an important clinical fact: There is a great deal of heterogeneity in the response of glycemia to the same dietary intervention across individuals. It implies that no universal coarse-grain formula can be applied to all users, and therefore, closed-loop systems must be used to learn personalized metabolic patterns based on individual response curves. Multimodal sensors embedded in smartwatches are further additions to this framework that offer other dimensions of data such as heart rate variability, sleep staging, and activity levels to evaluate the autonomic nervous function and circadian phase concurrently with glycemic parameters. Analyzing these multimodal data streams using deep learning models with transfer learning, the system can predict glycemic trends in real-time under different dietary and exercise conditions and iteratively enhance its predictive performance and adaptability. Real-world evidence demonstrates that real-time CGM itself is a behavioral intervention, enabling independent lifestyle changes in both prediabetic and type 2 diabetic individuals. The value of closed-loop systems is to upgrade the conventional "manual data analysis and adjustment" approach to an intelligent decision-making process. Here, algorithms automatically interpret data and trigger fine-tuning of formulations. For instance, they may elevate the content of resistant starch in breakfast coarse grains after successive postprandial glucose elevations, or replace dinner with a combination of calming grains containing GABA when prolonged low heart rate variability indicates stress. And the accurate assessment of glycated hemoglobin and glycemic variability by non-invasive wearable devices greatly reduces long-term physiological costs. This opens the door to closed-loop systems to move beyond clinical settings and into health management. Since the "monitor-analyze-adjust" closed-loop is continuously running on daily cycles, the metabolic feedback data from each user is used to refine the algorithmic model. This converts dietary prescriptions from static products to a co-evolving metabolic control system, thus progressing the technical vision of personalised nutrition strategies ("one person, one policy; one moment, one policy") towards engineering design.

The closed-loop precision nutrition system described here should be understood as a longer-term technological trajectory rather than a near-term clinical reality. Substantial technical validation is still required, particularly with respect to the robustness of AI models across diverse populations, the reliability of sensor data in free-living conditions, and the establishment of

data governance frameworks that ensure user privacy and safety. Professional oversight will remain essential, and autonomous algorithmic decision-making should not be implemented without rigorous prospective validation and regulatory approval. We suggest that the most productive near-term applications of these technologies are in supporting human decision-making, such as providing real-time feedback to patients and clinicians, rather than in autonomous algorithmic control.

5.3.2 Gut microbiota-metabolism digital twin

A gut microbiome-metabolic digital twin, digital gut twin, is an advanced technological framework that integrates individual microbiome profiles, dietary intake, host multi-omics data, and clinical information into a dynamic simulation platform. It allows different diet plans to be evaluated computationally to predict changes in gut bacterial structure and metabolic outputs, helping guide personalized nutrition. Microbial community-scale metabolic modeling (MCMC) uses species abundance from metagenomic/16S sequencing combined with genome-scale metabolic networks (GEMs) to simulate steady-state growth of the microbiome and production of postbiotics such as short-chain fatty acids (SCFAs) under specific dietary substrates, using constraint-based optimization methods such as flux balance analysis (FBA). Studies have found that the butyrate production predicted by MCMC was significantly negatively correlated with cardiovascular metabolic indicators such as C-reactive protein, LDL, blood pressure, and BMI, with greater predictive reliability in communities of higher microbial diversity, whereas directly measured plasma butyrate concentrations were not significantly associated with these markers, underscoring the unique value of predicting *in situ* production rates over static concentration measurements. Other studies have developed a deep-learning model based on a coupled multilayer perceptron to predict individual metabolite responses to specific dietary interventions from baseline gut microbiota composition and metabolomic data, demonstrating that it performed better than traditional machine learning methods in multiple population intervention trials. Other studies have combined metabolic network-derived features with algorithms such as XGBoost to construct a rapid prediction tool for butyrate production, which can screen thousands of candidate microbial communities in seconds after training. Digital twin technology makes it possible for individuals to explore the best diet plans in the digital space at a very low cost, but clinical applications are still limited by challenges such as insufficient coverage of metabolic databases, small training samples, and model interpretability.

6 Conclusion and future priorities

This view has methodically outlined the paradigm shift of coarse grains as traditional dietary staples to vehicles of precision health intervention. We have suggested a shift in thinking about five grains as nourishment to five grains as medicine, which does not imply that coarse grains are equivalent to pharmaceutical drugs but instead reclassifies them into a continuum of functionality between simple nutrition and data-driven, precision intervention. The overall roadmap of this paradigm shift includes the scientific decoding of traditional concepts of efficacy with metabolomics and gut microbiota studies, the creation of precision quantification systems in different populations, the investigation of specific applications throughout the lifespan and across different disease settings, and the reinvention of industrial

ecology and technological innovation. Nevertheless, as highlighted all through this Perspective, this vision is aspirational and will need a lot of evidence generation, technology development and policy innovation before it can be translated into routine practice.

There are five priority areas of future research and development that need special attention. First, the development of multi-omics integrated evaluation systems necessitates harmonized analytical pipelines, population-specific reference metabolome databases, and well-powered intervention studies. Second, clinical validation of the "first therapeutic meal" approach requires well-designed randomized controlled trials in various metabolic phenotypes with long-term follow-up. Third, the design of data-driven closed-loop precision nutrition frameworks requires prospective validation of AI algorithms, data governance policies and clinical utility. Fourth, to develop standardization frameworks of FMH products, minimum effective levels of bioactive components, validated analytical methods and tiered product classification systems are needed. Fifth, international collaborative studies with harmonized protocols and adaptation of intervention strategies to local dietary cultures are required to generate cross-cultural evidence of coarse grain interventions. To sum up, the paradigm shift in food to medicine at the coarse grain level is not a vision but an emerging reality at the intersection of nutritional science, biomedical research, data technology, and industrial innovation. Through the creation of strict evidence-based frameworks, promotion of technological advancement, creation of suitable regulatory and policy channels, and honoring the rich cultural heritage of dietary therapy, we can unleash the full potential of coarse grains as a means of preventing and managing chronic diseases, leading to healthier communities and more sustainable food systems.

Data availability

Not applicable.

Conflicts of interest

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None.

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