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Artificial Intelligence-Enabled Precision Functional Foods for Drug-Resistant Epilepsy: Bridging Next-Generation Food Processing, Gut-Brain Axis Modulation, and Intracranial Electrophysiology

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Abstract

Despite significant advancements in antiseizure medications and surgical interventions, drug-resistant epilepsy continues to affect approximately one-third of all epilepsy patients. While intracranial stereoelectroencephalography and subsequent resection effectively target focal epileptogenic zones, these invasive interventions fail to address the systemic neuroinflammation and network-level hyperexcitability that drive seizure chronicity. Emerging evidence highlights the microbiota gut-brain axis as a critical modulator of this systemic milieu, where intestinal dysbiosis and disrupted blood-brain barrier integrity lower the seizure threshold. This comprehensive review proposes a novel, interdisciplinary paradigm that shifts the focus from traditional, broadly restrictive diets to artificial-intelligence-driven precision nutrition implemented through next-generation food processing technologies. We specifically explore how advanced fermentation, microencapsulation, and nanoemulsion techniques can engineer prescription grade functional foods (medical foods with standardized bioactive content), including customized synbiotics and bioavailable medium chain triglycerides, to restore microbial homeostasis and suppress microglial activation. Recent evidence demonstrates that dietary fiber content in ketogenic formulations significantly modifies gut microbiome composition and seizure resistance through microbial pathways independent of ketosis intensity, underscoring the potential of precision food engineering. Furthermore, we emphasize the revolutionary role of artificial intelligence in

analyzing patient specific multi-omics data to compute and match individualized neuro-nutritional formulations. Machine learning algorithms enable the transition from empirical dietary trials to predictive, computationally optimized interventions. These approaches essentially create digital gut twins that mirror patient specific metabolic requirements. Finally, we establish the necessity of bridging food science with clinical neurophysiology by utilizing continuous scalp electroencephalography and invasive stereoelectroencephalography as objective, quantifiable biomarkers. Clinicians can rigorously validate the neuromodulatory efficacy of precision functional foods through monitoring of interictal epileptiform discharges and high-frequency oscillations. Ultimately, the convergence of artificial intelligence, advanced food technology, and high-resolution electrophysiology offers a transformative, non-invasive adjunctive strategy for managing drug-resistant epilepsy, paving the way for precision neuro-nutrition. This paradigm directly addresses frontier areas in food science, including artificial intelligence and precision food technology, next-generation food processing, and gut-brain axis innovations, while establishing regulatory frameworks for clinical grade functional foods in neurological care.

Keywords

Artificial Intelligence, Precision Nutrition, Next-Generation Food Processing, Drug-Resistant Epilepsy, Gut-Brain Axis, Functional Foods, Stereo-Electroencephalography (SEEG), Microbiome, Medium-Chain Triglycerides, Microencapsulation

1. Introduction

Drug-resistant epilepsy, typically defined as failure to achieve sustained seizure freedom after adequate trials of two or more appropriate antiseizure medications, affects a substantial fraction of patients, with recent meta analyses indicating that approximately 30% of all individuals with epilepsy meet criteria for drug resistance despite optimal pharmacotherapy [1] [2]. This persistent epilepsy burden persists even in specialized surgical centers. A comprehensive 15-year surgical cohort analysis revealed that only 57.5% of patients achieved sustained seizure freedom following resective epilepsy surgery, leaving a significant proportion with continued breakthrough seizures [3]. The limitations of current therapeutic approaches highlight the urgent need for novel adjunctive strategies that address the multifactorial nature of epileptogenesis.

Contemporary clinical practice utilizes intracranial stereoelectroencephalography and subsequent resective or thermocoagulative surgery to precisely localize and eliminate focal epileptogenic zones. However, these invasive interventions primarily target anatomically defined seizure origins and cannot modify the patient's global brain milieu, such as widespread neurotransmitter imbalances, chronic neuroinflammation, and dysfunctional neural networks, that underlies seizure

generation and propagation [3] [4]. Advances in neuroimmunology have established that neuroinflammation represents a fundamental driver of epileptogenesis and seizure chronicity, with activated microglia, elevated pro-inflammatory-cytokines, and complement cascade activation acting as disease amplifiers that sustain and worsen epileptic networks even after initial insults [5]-[7]. Focal surgical treatments do not directly address these diffuse pathophysiological processes, which may explain why many patients experience relapse or fail to attain complete seizure freedom. Consequently, there is growing recognition that effective drug-resistant epilepsy management requires systemic, noninvasive therapies capable of modulating network-level pathological factors.

In parallel with these neuroscience advances, the microbiota gut-brain axis (MGB axis) has emerged as a critical conceptual framework linking dietary inputs, immune signaling, and central nervous system function. Decades of research now demonstrate that the trillions of microbes residing in the gastrointestinal tract communicate bidirectionally with the brain via metabolic, immune, endocrine, and neuronal pathways [8] [9]. Notably, diet represents one of the principal modulators of gut ecology, meaning that nutritional interventions can rapidly reshape microbial metabolite profiles and systemic immune tone [8] [9]. Recent comprehensive reviews have specifically implicated gut microbiome alterations in refractory epilepsy. Patients with drug-resistant epilepsy frequently exhibit intestinal dysbiosis characterized by reduced diversity and altered composition of beneficial taxa, while microbiome targeted interventions, including the ketogenic diet and probiotic supplementation, correlate with measurable seizure reduction [1] [10].

The mechanistic links between intestinal dysbiosis and cortical hyperexcitability are increasingly well defined. Dysbiosis induced compromise of intestinal barrier integrity permits translocation of immunogenic microbial components, such as lipopolysaccharides, into systemic circulation, triggering innate immune responses and cytokine cascades that compromise blood-brain barrier function [11]. Peripheral inflammatory mediators subsequently infiltrate the central nervous system, activating microglia and disrupting the delicate balance between excitatory and inhibitory neurotransmission [12]. Under physiological conditions, microbiome derived short-chain fatty acids, particularly butyrate, propionate, and acetate, maintain microglia in homeostatic, neuroprotective states through histone deacetylase inhibition and promotion of neurotrophic factor expression [13] [14]. In drug-resistant epilepsy, depletion of short-chain fatty acid producing taxa, such as *Faecalibacterium prausnitzii* and *Roseburia* species, removes this inhibitory control, enabling microglial activation that enhances glutamatergic excitation while impairing GABAergic inhibition [15]-[17].

Building upon these mechanistic insights, next-generation food processing technologies are enabling unprecedented precision in nutritional interventions. Modern advances in fermentation technology, microencapsulation, and synthetic biology facilitate creation of customized prebiotic probiotic combinations known as synbiotics, fermentation derived bioactives, and medium chain triglyceride

formulations specifically engineered to target neuronal metabolism and neuroinflammatory pathways [18]-[20]. These innovations address critical limitations of traditional dietary therapies. Whereas the classic ketogenic diet, despite its proven efficacy, suffers from poor long term adherence due to rigid macronutrient restrictions and adverse metabolic effects, precision engineered functional foods enriched with medium chain triglycerides or tailored polyphenols can achieve similar neuroprotective outcomes with substantially improved palatability and compliance [21]-[23].

Recent groundbreaking research has further illuminated how dietary fiber content specifically modulates the anti-seizure efficacy of ketogenic formulations. A 2025 study by Özcan and colleagues demonstrated that dietary fiber content, rather than fat ratio or source, drives substantial metagenomic shifts that determine seizure resistance in mouse models [24]. Fiber supplementation restored seizure protective effects in fiber deficient ketogenic formulas and potentiated anti-seizure efficacy in fiber containing formulations through enrichment of specific microbial pathways, including queuosine biosynthesis and alterations in glutamate and GABA metabolism, independent of ketosis intensity [24]. These findings underscore the potential of precision food engineering to optimize therapeutic outcomes through targeted manipulation of microbiome accessible carbohydrates.

Realizing the full potential of precision nutrition requires sophisticated personalization capabilities that exceed traditional dietary assessment methods. Here, artificial intelligence and machine learning play transformative roles by enabling analysis of complex, multi dimensional datasets that integrate host genomics, metabolomics, and high-resolution gut microbiome profiles [25] [26]. AI driven precision nutrition frameworks leverage systems biology models to tailor interventions to individual host microbiome ecosystems, with recent applications demonstrating improved glycemic control, metabolic health outcomes, and dietary adherence compared to standard approaches [25]. For epilepsy specifically, machine learning algorithms can identify predictive correlations between microbial signatures, neuroinflammatory markers, and epileptogenic susceptibility, enabling computation of optimal functional food matrices for individual patients [26] [27].

The convergence of these technological advances necessitates rigorous validation methodologies that bridge food science and clinical neurophysiology. Electroencephalography, particularly continuous scalp monitoring and invasive stereoelectroencephalography, provides objective, quantifiable biomarkers for assessing the neuromodulatory effects of nutritional interventions [28] [29]. Changes in interictal epileptiform discharges, high-frequency oscillations, and background rhythmic activity offer direct evidence of how precision functional foods influence cortical excitability and epileptic network dynamics [30] [31]. By correlating food induced metabolic changes with electrophysiological outcomes, clinicians can establish closed-loop systems for refining dietary strategies and predicting long term seizure control.

This review synthesizes current evidence supporting the integration of next-generation food processing, AI driven personalization, and intracranial electrophysiology into a comprehensive framework for drug-resistant epilepsy management. We examine the pathophysiological mechanisms linking gut dysbiosis to seizure susceptibility, explore technological innovations in functional food engineering, detail the application of machine learning for precision nutritional formulation, and establish EEG and stereoelectroencephalography based methodologies for objective efficacy validation. Ultimately, we propose that this interdisciplinary convergence represents a paradigm shift from treating epilepsy purely as an isolated electrical anomaly to managing it as an interconnected, systemic network disorder, offering new hope for the substantial population of patients with drug-resistant seizures.

2. The Gut-Brain Axis in Epilepsy: Pathophysiological Mechanisms and Systemic Inflammation

The MGB axis represents a highly integrated, bidirectional communication network that connects the enteric nervous system and intestinal microenvironment with the central nervous system. In recent years, an accumulating body of evidence has highlighted this axis as a critical modulator of neurological health, with profound implications for epileptogenesis and seizure chronicity [8]. In patients with drug-resistant epilepsy, widespread alterations in microbial diversity and composition, termed intestinal dysbiosis, are frequently observed, shifting the paradigm of epilepsy from a strictly localized cortical pathology to a systemic network disorder.

The primary mechanism linking gut dysbiosis to cortical hyperexcitability is systemic inflammation driven by compromised intestinal barrier integrity. A healthy microbiome maintains the tight junctions of the intestinal epithelium. However, dysbiosis frequently leads to increased intestinal permeability, colloquially known as leaky gut. This structural breakdown permits the translocation of immunogenic microbial components, such as lipopolysaccharides, into the systemic circulation [11]. The influx of lipopolysaccharides initiates a robust innate immune response, triggering the release of pro-inflammatory-cytokines, including interleukin 6, interleukin 1 beta, and tumor necrosis factor alpha.

Crucially, this systemic inflammatory cascade does not remain confined to the periphery. Circulating cytokines and microbial antigens interact with the blood-brain barrier, compromising its endothelial tight junctions and increasing its permeability. Once the blood-brain barrier is breached, peripheral inflammatory mediators infiltrate the central nervous system, where they exert profound neuromodulatory effects, primarily through the activation of microglia [12].

Microglia, the resident immune cells of the brain, are highly sensitive to signals from the gut microbiome. Under physiological conditions, microbiome derived metabolites, particularly short-chain fatty acids such as butyrate, propionate, and acetate, cross the blood-brain barrier and maintain microglia in homeostatic,

neuroprotective states. Short-chain fatty acids act as histone deacetylase inhibitors, suppressing neuroinflammatory pathways and promoting the expression of neurotrophic factors [13] [14]. In the dysbiotic state typical of drug-resistant epilepsy, the depletion of short-chain fatty acid producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia* species, removes this inhibitory control. Consequently, microglia assume a reactive, pro inflammatory phenotype.

Activated microglia fundamentally alter synaptic transmission and cortical excitability. They release neurotoxic factors and excitatory amino acids, such as glutamate, while simultaneously downregulating the expression of astrocytic glutamate transporters, leading to toxic extracellular glutamate accumulation. Furthermore, neuroinflammation impairs GABAergic inhibitory signaling. This dual effect, enhancing glutamatergic excitation and dampening GABAergic inhibition, drastically lowers the seizure threshold and facilitates the synchronous, abnormal neuronal discharges characteristic of epileptic networks [7] [8]. Therefore, modulating the intestinal microenvironment to restore short-chain fatty acid production and suppress microglial activation presents a highly rational adjunctive therapeutic target for drug-resistant epilepsy.

Recent advances in understanding short-chain fatty acid production pathways have revealed the complexity of microbial metabolism relevant to epilepsy management. Short-chain fatty acids are generated through anaerobic fermentation of dietary fibers by specialized gut bacteria, with production rates and profiles determined by substrate availability, microbial composition, and colonic transit time [32]. The major short-chain fatty acid producing bacteria belong to Clostridium clusters (groups IV and XIVa), including *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Roseburia* species, and *Ruminococcus bromii*, which together account for 60 to 80 percent of colonic butyrate production [32]. Distinct substrates yield specific short-chain fatty acid profiles. Resistant starch preferentially promotes butyrate synthesis through cross feeding interactions involving *Ruminococcus bromii* and *Eubacterium rectale*, whereas pectin and arabinoxylans favor acetate production by *Bacteroides* species [32]. These insights provide a mechanistic foundation for precision food engineering targeting specific microbial pathways in epilepsy patients.

3. Next-Generation Food Processing and Functional Interventions: Targeted Neuromodulation

3.1. Precision Fermentation for Neuroactive Metabolite Production

Although the classic ketogenic diet has been utilized for nearly a century to manage refractory seizures, its clinical utility remains severely limited by poor long-term adherence. The ketogenic diet's rigid carbohydrate restrictions often lead to gastrointestinal distress, dyslipidemia, and significant decreases in patient quality of life [22]. To overcome these limitations, the convergence of food science and neurology has birthed a new paradigm: using next-generation food processing

technologies to engineer functional foods that mimic the neuroprotective effects of the ketogenic diet without its restrictive drawbacks.

Foremost among these innovations is the application of advanced fermentation technology and precision bioprocessing. Traditional fermentation relies on spontaneous or broadly inoculated microbial cultures, but next-generation precision fermentation utilizes specific, genetically characterized microbial consortia designed to optimize the yield of neuroactive metabolites. Through controlled biotransformation, food matrices can be pre-digested and enriched with exceptionally high concentrations of short-chain fatty acids, particularly butyrate, and neuroactive peptides [23]. Recent studies demonstrate that precision fermentation can generate bioactive compounds with significant health promoting properties, including antioxidant and anti-inflammatory effects that modulate blood glucose and lipid profiles [23] [25]. The fermentation enhanced antioxidant potency of specific metabolites positions these compounds as key mediators for targeting oxidative-stress-induced neuroinflammation via the gut-brain axis [23] [25].

3.2. Advanced Microencapsulation and Synbiotic Delivery Systems

Use either SI (MKS) or CGS as primary units. (SI units are encouraged.) English units may be used as secondary units (in parentheses). An exception would be the use of English units as identifiers in trade, such as "3.5-inch disk drive". Furthermore, advanced microencapsulation and nanoemulsion technologies have revolutionized the delivery of probiotics and prebiotics, known as synbiotics. A major challenge in conventional probiotic administration is the degradation of beneficial bacteria by gastric acid and bile salts before reaching the colon. Next-generation processing encapsulates custom formulated probiotic strains, such as targeted *Lactobacillus* and *Bifidobacterium* species known for high GABA or short-chain fatty acid production, within specialized biopolymer matrices. These matrices ensure targeted release in the lower intestine, facilitating successful colonization and immediate modulation of the local immune environment [27] [33].

Recent advances in microencapsulation technology have introduced sophisticated targeting mechanisms for inflammatory conditions. Encapsulation materials can be functionalized with small molecule targeting ligands, such as hyaluronic acid, peptides, or folate, to enable specific binding to receptors overexpressed at inflamed sites, facilitating probiotic accumulation in these regions [34]. Studies demonstrate that hyaluronic-acid-functionalized nano-armored probiotics (bacteria protected by nanoscale coatings) exhibit resistance to harsh gastrointestinal environments and preferential mucoadhesive capacity under inflammatory conditions, releasing bacteria in a timely manner to ameliorate pathological inflammation [34]. These technologies provide a promising template for targeting the gut inflammation characteristic of drug-resistant epilepsy, potentially enabling precision delivery of anti-inflammatory bioactives to the intestinal mucosa.

3.3. Medium Chain Triglyceride Formulations and Ketone Body Metabolism

Another pivotal breakthrough is the development of intelligently formulated foods enriched with medium chain triglycerides. Unlike long chain fatty acids, medium chain triglycerides bypass the lymphatic system and are transported directly to the liver, where they are rapidly metabolized into ketone bodies, such as beta hydroxybutyrate, even in the presence of dietary carbohydrates. This pharmacokinetic advantage allows for the induction of mild, sustained ketosis, providing alternative energy substrates to functionally compromised epileptic neurons and exerting direct anti-seizure effects, without requiring the extreme carbohydrate deprivation of a classic ketogenic diet [35]. Recent research confirms that medium chain triglyceride supplementation protects against epilepsy associated behavioral impairments in mouse models by modulating mTOR and Gsk 3β signaling pathways [35].

Through innovations like lipid nanoemulsions, food scientists can now mask the inherent astringency of medium chain triglycerides, incorporating them seamlessly into palatable functional beverages, yogurts, or medical foods. This drastically improves patient compliance and tolerability. Ultimately, these next-generation food processing techniques enable a shift from the blunt instrument of systemic dietary restriction to highly targeted, bioavailable, and patient friendly functional interventions. By directly addressing the gut-brain axis deficits identified in drug-resistant epilepsy, these engineered foods offer a sustainable, non-pharmacological avenue to elevate seizure thresholds and improve clinical outcomes following stereoelectroencephalography evaluation.

4. Artificial Intelligence and Precision Food Technology: Computing the Optimal Neuro-Nutritional Matrix

4.1. Machine Learning Algorithms for Multi-Omics Data Integration

The extreme inter individual variability of the human gut microbiome presents a profound challenge to standardized dietary interventions. A functional food that effectively modulates the MGB axis in one patient with drug-resistant epilepsy may be entirely inefficacious in another due to distinct baseline dysbiosis. To overcome this, the integration of artificial intelligence and machine learning into nutritional science has catalyzed the transition from population based dietary guidelines to hyper personalized precision nutrition [26] [36].

Artificial intelligence fundamentally alters the development of targeted nutritional therapies by providing the computational power necessary to decode complex multi-omics datasets. When evaluating a drug-resistant epilepsy patient, clinicians can now gather high dimensional data, including host genomics, metabolomics, and, most crucially, high throughput microbial sequencing techniques (16S rRNA or whole metagenome sequencing) of the patient's gut microbiota. However, analyzing the non-linear, multi-layered interactions within this biological

data exceeds human cognitive capacity. Advanced machine learning algorithms, particularly deep neural networks and random forest classifiers, excel at identifying hidden patterns within these vast microbial landscapes [25] [26] [37] (**Figure 1**).

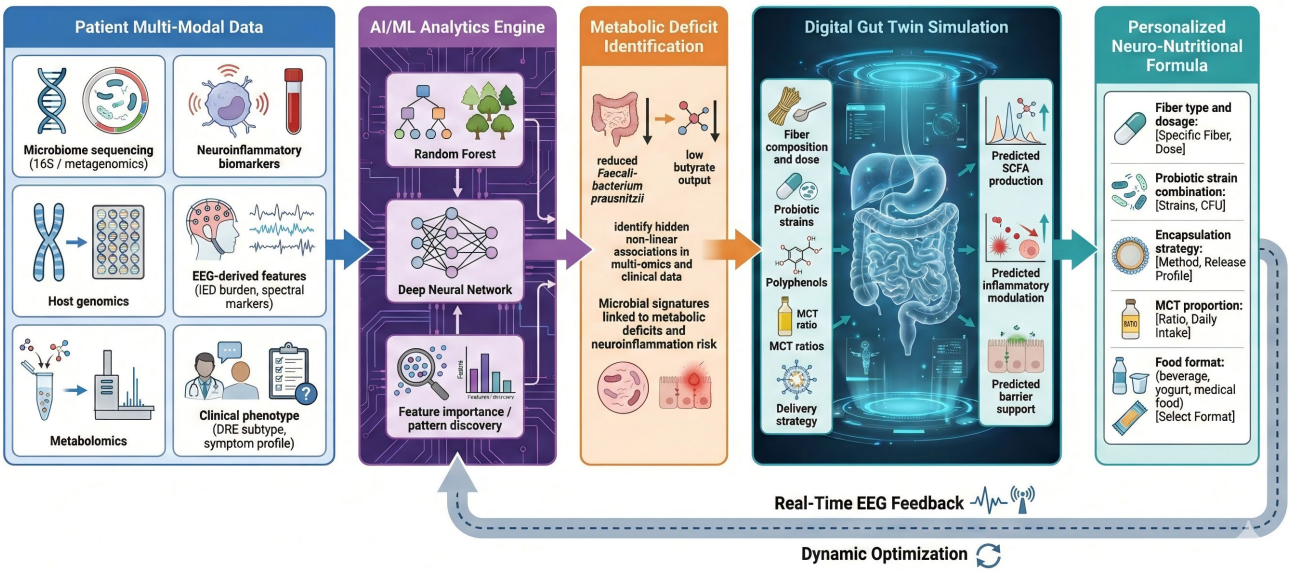

Figure 1. Artificial intelligence-enabled precision nutrition framework for drug-resistant epilepsy.

4.2. From Biological Correlations to AI-Driven Metabolic Deficit Identification

Emerging evidence has established robust biological correlations between specific microbial signatures, neuroinflammatory markers, and epileptogenic susceptibility in neurological patients [38]. Specifically, clinical and experimental studies demonstrate that an underrepresentation of *Faecalibacterium prausnitzii* leads to insufficient central nervous system butyrate levels, a key metabolic deficit in epilepsy pathogenesis [39] [40]. Leveraging these well-characterized relationships, artificial intelligence models trained on large cohorts hold the potential to parse an individual patient's microbiome profile and identify such precise metabolic deficits. Furthermore, recent studies have demonstrated the significant potential of AI and machine learning technologies in personalized nutrition, with random forest classifiers achieving high accuracy in predicting optimal dietary interventions [25] [37].

4.3. Digital Twin Modeling and Personalized Formulation

Once the precise microbial deficit is mapped, artificial intelligence systems can transition from diagnostic to prescriptive roles. Computational platforms can simulate millions of interactions between the patient's baseline microbiome and various next-generation food components, such as specific prebiotic fibers, polyphenols, or medium chain triglyceride combinations. The algorithm effectively computes and matches the optimal functional food matrix required to rescue the

patient's specific dysbiotic profile [36] [39] [41]. This in silico modeling creates a digital twin of the patient's gut, enabling food scientists to engineer a bespoke nutritional formulation, a precise combination of biotics and energy substrates, designed specifically to upregulate neuroprotective metabolites, repair the blood-brain barrier, and ultimately stabilize the patient's hyperexcitable neural networks.

4.4. Deep Learning for Real-Time EEG Monitoring and Feedback

Recent advances in deep learning for electroencephalogram analysis further enhance the precision nutrition framework. Deep learning algorithms have shown potential in automating the detection of interictal epileptiform discharges, with convolutional neural networks achieving expert level performance [42]. These algorithms can process continuous electroencephalogram recordings to provide real-time feedback on neurological status, enabling dynamic adjustment of nutritional interventions based on objective biomarkers rather than subjective seizure diaries [42].

5. EEG and SEEG as Objective Biomarkers for Nutritional Efficacy: Bridging Neurophysiology and Food Science

5.1. Scalp EEG and Interictal Epileptiform Discharges as Surrogate Markers

While the theoretical framework for artificial-intelligence-driven functional foods is robust, validating their clinical efficacy requires rigorous, objective quantification. Historically, nutritional interventions in epilepsy have been evaluated primarily through patient reported seizure diaries. However, these diaries are notoriously subjective, prone to recall bias, and fail to capture subclinical epileptic activity [43]. To truly bridge clinical neurophysiology with food science, electroencephalography, particularly continuous scalp EEG and invasive stereoelectroencephalography, must be repurposed as dynamic biomarkers for nutritional efficacy [42]-[44].

Scalp EEG provides a continuous, non invasive window into cortical excitability. When a targeted functional food intervention is initiated to suppress systemic neuroinflammation, its neuromodulatory effects can be quantitatively tracked via changes in interictal epileptiform discharges. Interictal epileptiform discharges, such as isolated spikes, polyspikes, and sharp waves, are subclinical electrical anomalies that serve as reliable surrogate markers for the epileptogenic propensity of the underlying network. By utilizing automated, artificial intelligence assisted EEG signal processing, clinicians can continuously monitor the frequency, spatial distribution, and amplitude of interictal epileptiform discharges before, during, and after the dietary intervention [45]. A statistically significant reduction in interictal epileptiform discharge burden over a defined nutritional trial period provides objective, measurable proof that the precision food matrix is successfully altering brain electrochemistry [36].

Recent advances in deep learning have enabled expert level detection of interictal epileptiform discharges. Studies demonstrate that deep neural networks can detect interictal epileptiform discharges on par with clinical experts, with sensitivities exceeding 82 percent at high specificity [45]. These algorithms may support visual EEG analysis and assist in diagnostics, particularly when human resources are limited, enabling scalable monitoring of nutritional interventions across large patient populations [45].

5.2. SEEG, HFOs, and Wearable EEG for Deep Brain Monitoring

Furthermore, in the context of patients undergoing presurgical evaluation or those who have had temporary neurostimulation electrodes implanted, stereoelectroencephalography offers unprecedented spatio-temporal resolution. Stereoelectroencephalography allows for the direct recording of deep cortical and subcortical structures, bypassing the spatial attenuation of the skull [46]. This is particularly crucial for evaluating high-frequency oscillations, which are increasingly recognized as highly specific biomarkers of epileptogenic tissue [47] [48].

High-frequency oscillations, encompassing ripples and fast ripples, represent distinct patterns of epileptic activity that can guide surgical planning. A systematic review of 13 studies focusing on high-frequency oscillations confirmed the potential interest of fast ripples to delineate the epileptogenic zone, with a pooled sensitivity of 0.8, a pooled specificity of 0.72 and an area under the curve of 0.82 [47]. By integrating stereoelectroencephalography data with precision nutrition, researchers can observe the localized effects of gut derived metabolites, like short-chain fatty acids, on deep brain structures such as the hippocampus or amygdala in real-time. If a customized, artificial intelligence matched functional food regimen successfully reduces microglial activation and lowers extracellular glutamate, this should be directly reflected by a suppression of pathological high-frequency oscillations and a normalization of background rhythmic activity on the stereoelectroencephalography tracings.

Recent studies have compared various interictal stereoelectroencephalography biomarkers and found that spike-ripples best identify the epileptogenic zone [47]. This finding suggests that composite biomarkers combining traditional spikes with high-frequency activity may offer superior sensitivity for detecting subtle neuromodulatory effects of nutritional interventions.

The integration of wearable EEG technologies further extends monitoring capabilities beyond inpatient settings. Novel mobile and portable EEG solutions designed for short and long term monitoring of individuals with epilepsy have been developed, with healthcare professionals emphasizing the need for high performance, data quality, easy patient mobility, and comfort as crucial features for these devices [49]. These wearable systems allow for continuous, ambulatory quantification of how daily functional food consumption impacts interictal epileptiform discharges over months or years, providing essential temporal data for refining artificial-intelligence-driven nutritional algorithms and establishing dose response

relationships between specific bioactive compounds and electrophysiological outcomes.

Ultimately, utilizing continuous EEG, stereoelectroencephalography, and wearable technologies as quantitative biomarkers transforms nutritional psychiatry from an observational field into a hard, measurable science. It provides the crucial feedback loop required to validate artificial intelligence predictions, refine customized food formulas, and conclusively demonstrate that next-generation food processing technologies can exert potent, measurable, and targeted neuromodulatory effects on the human brain.

6. Conclusion and Future Perspectives: A New Collaborative Horizon

6.1. Summary of the Integrated Paradigm

The management of drug-resistant epilepsy currently stands at a critical inflection point. The traditional dichotomies of neurology, separating central nervous system pathology from systemic gastrointestinal health, and isolating pharmacological treatments from dietary interventions, are no longer tenable. As this review has outlined, the MGB axis operates as a fundamental, bidirectional driver of neuroinflammation and cortical excitability. Addressing drug-resistant epilepsy through strictly focal, resective means often leaves the underlying systemic drivers unchecked, contributing to post surgical relapse.

The integration of next-generation food processing, artificial intelligence, and clinical neurophysiology offers a paradigm shifting adjunctive approach. By leveraging precision fermentation and advanced microencapsulation, food science can now produce functional interventions that deliver the potent neuromodulatory benefits of traditional dietary therapies without their restrictive, compliance limiting drawbacks. However, the true potential of these technologies can only be unlocked through personalization. Artificial intelligence and machine learning are the indispensable engines of this personalized approach, capable of decoding the immense complexity of the human microbiome to compute bespoke nutritional matrices tailored to a patient's unique neuro metabolic deficits.

6.2. Priority Research Initiatives

Looking forward, realizing the full clinical potential of artificial-intelligence-driven precision nutrition in epilepsy requires a concerted, cross disciplinary effort. Future research must prioritize the following initiatives.

First, large scale multi-omics databanks must be established. The creation of expansive, open access repositories correlating microbiome profiles, metabolomics, and longitudinal stereoelectroencephalography data in drug-resistant epilepsy patients is essential. These datasets are necessary for training more robust, highly predictive artificial intelligence models capable of identifying nuanced epileptogenic biomarkers within the gut.

Second, longitudinal clinical trials with wearable technology must be conducted.

Moving beyond acute, inpatient EEG monitoring to incorporate ultra long term, minimally invasive, or wearable EEG devices will allow for the continuous, real-world quantification of how daily functional food consumption impacts interictal epileptiform discharges over months or years. Recent surveys of healthcare professionals indicate high interest in integrating these novel systems into clinical practice, particularly for supervising drug-resistant epilepsy, reducing sudden unexpected death in epilepsy, and detecting nocturnal seizures [19].

Third, regulatory and manufacturing frameworks must be developed. Standardized protocols for the clinical validation and quality control of prescription grade functional foods and customized probiotics must be established, ensuring they meet the stringent safety and efficacy standards required for neurological adjunctive therapies. The translation of artificial intelligence designed functional foods into clinical practice necessitates novel regulatory frameworks. Unlike conventional nutraceuticals, precision nutritional interventions for drug-resistant epilepsy would function as adjunctive medical therapies, requiring FDA or EMA classification distinct from standard dietary supplements.

Fourth, three-dimensional food printing of personalized nutritional matrices represents an emerging technological frontier. While currently experimental, artificial intelligence optimized three-dimensional printed foods could enable precise spatial distribution of multiple bioactive compounds, including ketone precursors, specific short-chain fatty acids, and anti-inflammatory polyphenols, within a single meal structure, tailored to an individual's circadian seizure patterns and microbiome diurnal rhythms.

6.3. Final Remarks

Finally, closed-loop systems integrating real-time EEG monitoring with automated nutritional adjustment algorithms should be developed. Such systems would enable dynamic optimization of functional food formulations based on continuous neurophysiological feedback, representing the ultimate realization of precision neuro-nutrition.

In conclusion, the intersection of advanced food technology and neuroscience represents a fertile frontier for epilepsy management. By deploying artificial intelligence to guide nutritional interventions and utilizing high resolution EEG and stereoelectroencephalography to objectively validate their efficacy, the scientific community can transition from treating epilepsy purely as an isolated electrical anomaly to managing it as an interconnected, systemic network disorder. This interdisciplinary convergence not only promises to enhance the quality of life for patients with drug-resistant epilepsy but also serves as a blueprint for the future of precision neuro-nutrition across a spectrum of neurological diseases.

The schematic illustrates the integration of multi-omics data analysis, machine learning algorithms, and digital twin modeling to compute personalized neuro-nutritional formulations. Patient-specific microbiome profiles, genetic variants, and metabolic markers are processed through deep neural networks and random

forest classifiers to identify precise metabolic deficits (e.g., *Faecalibacterium prausnitzii* depletion). Computational platforms simulate interactions between baseline microbiome and next-generation food components (prebiotic fibers, polyphenols, medium-chain triglycerides), creating a digital gut twin that mirrors individual metabolic requirements. The optimal functional food matrix is validated through continuous EEG monitoring of interictal epileptiform discharges (IEDs) and high-frequency oscillations (HFOs), establishing a closed-loop system for precision neuro-nutrition.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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