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Exploratory Dietary Approaches for Drug-Resistant Epilepsy Beyond Standard Ketogenic Diet and Fish Oil: A Systematic Review of Preliminary Clinical Evidence

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 December 2025 and was last updated on 31 December 2025.

INTRODUCTION

Review question / Objective The objective of this systematic review is to provide the first systematic evaluation of clinical evidence for emerging dietary interventions for epilepsy—specifically those other than the standard ketogenic diet (KD) and fish oil.

Rationale Necessary to synthesize disparate human studies, assess their quality (Risk of Bias), and provide clear, evidence-based guidance for clinical practice and future research.

Condition being studied The condition being studied in this systematic review is drug-resistant epilepsy (DRE).

METHODS

Search strategy Following PRISMA 2020 guidelines, a comprehensive literature search was conducted across multiple electronic databases including PubMed, Web of Science, the Cochrane Register of Studies, and Google Scholar for publications available up to March 2025. To identify ongoing or unpublished trials, we additionally searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

Participant or population For the Patient, Participant, or population (P) * field on the INPLASY form, you should provide a description that clearly defines who the subjects of the studies are. Based on your systematic review manuscript, here is the appropriate text:

Patient, Participant, or population (P) *
Target Population: Humans of any age diagnosed with epilepsy.
Clinical Condition: Specifically focusing on patients with drug-resistant epilepsy (DRE), defined as individuals who continue to experience seizures despite the use of antiepileptic drugs (AEDs).
Scope of Age: The review includes both pediatric populations (children) and adults.
Specific Sub-populations: The population includes patients with specific comorbidities, such as confirmed celiac disease, where epilepsy may manifest as a neurological symptom.
Total Sample Size: The synthesis encompasses a total of 675 epilepsy patients across the included human trials.
Eligibility Criteria Summary for this section:
Inclusion: Any human subject with a confirmed diagnosis of epilepsy regardless of age.
Exclusion: Animal models and case reports are excluded to prioritize structured human clinical evidence.

Intervention The systematic review evaluates "non-standard" dietary strategies for drug-resistant epilepsy that target novel pathophysiological pathways like the gut–brain axis and metabolic fuel shifts. These interventions include modified ketogenic protocols such as olive oil-based ketogenic diets , gut-microbiota modulators like probiotics and synbiotics , specific nutrient additions including Medium-Chain Triglyceride (MCT) oil and branched-chain amino acids (BCAAs) , as well as restrictive gluten-free or low glutamate diets. Notably, this review explicitly excludes standard classical ketogenic diets, modified Atkins diets, and isolated fish oil supplementation to focus on these emerging exploratory targets.

Comparator Comparators include no intervention, placebo , usual diet (regular diet without modifications) , or an active dietary intervention. Examples from the included studies include comparing a low-glutamate diet against a regular diet control group and comparing an MCT-based ketogenic diet directly against a classical vegetable oil-based ketogenic diet.

Study designs to be included The review includes Randomized Controlled Trials (RCTs) and Non-Randomized Studies of Interventions (NRSIs), such as quasi-experimental, prospective cohort, and single-arm pre-post intervention studies. To prioritize evidence from structured human trials and maintain methodological rigor, case reports and animal studies were explicitly excluded from the analysis.

Eligibility criteria The review includes Randomized Controlled Trials (RCTs) and Non-Randomized Studies of Interventions (NRSIs), such as quasi-experimental, prospective cohort, and single-arm pre-post intervention studies. To prioritize evidence from structured human trials, case reports and animal studies were explicitly excluded.

Information sources Comprehensive searches were conducted in electronic databases including PubMed, Web of Science, the Cochrane Register of Studies, and Google Scholar for studies published up to March 2025. To capture ongoing or unpublished research, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) were also searched. Additionally, the reference lists of all identified eligible articles were manually screened to ensure the inclusion of all relevant primary studies.

Main outcome(s) The primary outcomes focus on efficacy in seizure control, specifically measuring changes in seizure frequency from baseline to the end of the intervention11111. Key metrics include the responder rate, defined as the proportion of participants achieving a $\ge 50\%$ reduction in seizure frequency, and the rate of seizure freedom222222222. These outcomes are synthesized across various dietary interventions to evaluate their clinical effectiveness in managing drug-resistant epilepsy3333.

Quality assessment / Risk of bias analysis Two reviewers independently assessed the quality of included studies using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials and the ROBINS-I tool for non-randomized studies. Assessment domains included the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Discrepancies were resolved through consensus, and a sensitivity analysis was planned to include only studies at low risk of bias to determine the robustness of the findings.

Strategy of data synthesis A structured narrative synthesis was conducted with results grouped by the pre-specified dietary intervention category4. A formal meta-analysis was not performed due to substantial clinical diversity among interventions and high statistical heterogeneity ($I^2 > 80\%$) observed in preliminary analyses5555. The synthesis focused on a qualitative assessment of primary efficacy outcomes, including seizure frequency, responder rates, and seizure freedom,

while rigorously accounting for individual study risks of bias6.

Subgroup analysis Results are qualitatively synthesized and grouped by specific dietary intervention categories to account for the high clinical diversity of the included studies. These subgroups include modified ketogenic protocols (olive oil-based KD, MCT-based KD), gut–brain axis modulators (probiotics and synbiotics), nutrient supplements (BCAA and MCT oil additions), and restrictive diets (gluten-free for celiac disease and low glutamate diets). Each subgroup analysis evaluates primary efficacy outcomes—such as seizure frequency and responder rates—while considering the unique risk of bias and participant demographics associated with each distinct dietary strategy.

Sensitivity analysis A sensitivity analysis is planned to evaluate the robustness of the review's findings by including only those studies identified as having a low risk of bias. This analysis aims to determine if the preliminary signals of efficacy observed in the full dataset—particularly those from non-randomized studies with higher risk of bias—persist when restricted to higher-quality evidence.

Country(ies) involved China, USA.

Keywords Drug-resistant epilepsy; Ketogenic diet modifications; Probiotics; Gut–brain axis; Low glutamate diet; Systematic review.

Contributions of each author
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