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Evaluation the Efficacy of Nutritional Interventions in the Recovery and Management of Post-Concussion

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Abstract: Post-concussion syndrome (PCS) affects a substantial number of patients, often involves prolonged symptom duration, and imposes a considerable medical and economic burden. This study systematically evaluated the efficacy of nutritional interventions for PCS recovery compared to conventional treatments. Following PRISMA guidelines, a literature review identified nine studies that met inclusion criteria, examining the effects of interventions including melatonin, Enzogenol, MLC901, phytocannabinoids, and the ketogenic diet. Key findings indicated that melatonin improved sleep quality and alleviated PCS symptoms, MLC901 enhanced attention and executive functioning, Enzogenol reduced mental fatigue and promoted restorative sleep, a ketogenic diet improved visual memory, and phytocannabinoids mitigated autonomic dysfunction and related symptoms. Despite variability in study designs and limited sample sizes, nutritional interventions demonstrated promising benefits for PCS symptom management. Future research should prioritize large-scale, well-controlled trials with standardized protocols and long-term follow-up to validate these findings and inform clinical practice.

Keywords: post-concussion syndrome (PCS); nutritional intervention; cognitive recovery; systematic review

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1. Introduction

Post-concussion syndrome (PCS) is a potential long-term complication of traumatic brain injury (TBI) [1]. It is characterized by persistent physical, cognitive, and emotional symptoms that extend beyond the typical recovery period, and may arise after mild, moderate, or severe TBI [2]. Epidemiological data suggest a wide prevalence range, with estimates varying from less than 10% to over 50%, depending on the study population and diagnostic criteria. Beyond the personal burden, PCS imposes substantial economic costs, with estimates ranging from several thousand to tens of thousands of US dollars per patient [3]. In addition to these financial implications, PCS often necessitates prolonged social support and leads to significant productivity losses, affecting both patients and their families.

1.2. Definition and Diagnosing

TBI is most commonly caused by non-penetrating head trauma, falls, motor vehicle accidents, or sports-related injuries, and is typically classified according to the Glasgow Coma Scale (GCS) [4]. Patients with complex or multi-system injuries exhibit a higher susceptibility to developing PCS. Risk factors for PCS include biological sex, age, and pre-existing psychiatric or neurological conditions, with evidence suggesting that women and children are particularly vulnerable [5]. Although much research focuses on sports-related concussions, PCS is recognized across a broad spectrum of injury mechanisms,

underscoring the need for generalizable management strategies. Accurate diagnosis relies on clinical assessment, patient history, and, where appropriate, neuroimaging and neuropsychological testing.

1.3. Symptoms of PCS

PCS manifests as a heterogeneous constellation of symptoms, including dizziness, persistent fatigue, irritability, impaired attention and memory, sleep disturbances, and reduced stress tolerance [6]. In some cases, patients experience mood disorders, personality changes, or physical impairments such as headaches, visual disturbances, or balance issues. Longitudinal studies indicate that approximately 7-15% of individuals continue to experience symptoms beyond one-year post-injury [7]. Vulnerable populations-particularly women, older adults, and those with pre-existing mental health conditions-are more prone to anxiety, depression, and migraine, which can substantially diminish quality of life and functional independence.

1.4. The Role of Nutrition in PCS Recovery

The underlying pathophysiology of PCS remains incompletely understood. Proposed mechanisms include neurotransmitter dysregulation, persistent neuroinflammation, oxidative stress, and disrupted neurovascular function [8]. Given the brain's high metabolic demands and susceptibility to oxidative damage, nutritional interventions may offer a supportive avenue for recovery. While conventional treatment strategies rely heavily on pharmacological approaches that primarily provide symptomatic relief and carry potential side effects [9], nutritional therapies present complementary or alternative options. Compounds such as melatonin, Enzogenol, MLC901, ketogenic diets, and phytocannabinoids exhibit antioxidant, anti-inflammatory, and neuroprotective properties, suggesting potential utility in mitigating PCS symptoms and supporting cognitive recovery [10]. Despite growing interest, systematic evaluation of their clinical efficacy remains limited. This review synthesizes evidence from nine clinical trials to clarify the therapeutic potential and clinical role of these nutritional strategies in PCS management, highlighting gaps for future research.

2. Materials and Methods

2.1. Study Search and Selection Criteria

A comprehensive literature search was conducted across multiple electronic databases, including PubMed/MEDLINE, Web of Science, SPORTDiscus, CINAHL Complete, and Cochrane Reviews, following the PRISMA 2020 guidelines [11]. The search strategy was constructed using the Population, Intervention, Comparison, and Outcome (PICO) framework (Table 1) to ensure systematic identification of relevant studies. Keywords and MeSH terms related to post-concussion syndrome, mild traumatic brain injury, and nutritional interventions were combined using Boolean operators. Searches included articles published up to 2024, with no language restrictions, although non-English articles were translated when necessary. Detailed search strings, including synonyms and truncations, are provided in the supplementary materials to ensure reproducibility.

Table 1. PICO model and search strategy based on the PRISMA 2020 guidelines.

Component	Definition
Participants	Humans diagnosed with post-concussion syndrome (PCS) or experiencing persistent symptoms following mild traumatic brain injury (mTBI).
Intervention	Any nutrition- or diet-based intervention administered orally, including supplements, functional foods, or diet modifications.
Comparator	Placebo, standard care, pharmacological treatment, or no intervention.

Outcome	Any clinical or functional measure of PCS symptom recovery, including cognitive performance, mood, sleep quality, fatigue, or overall functional outcomes.

2.2. Selection Criteria and Study Selection

Eligible studies included randomized controlled trials (RCTs) and observational studies assessing the efficacy of nutritional interventions for PCS, with a particular focus on the chronic phase of mild TBI or concussion, defined as symptom persistence for at least one month [12]. Studies were required to report outcome measures reflecting symptom improvement and involve interventions administered orally. Exclusion criteria encompassed preclinical studies (animal or cell models), acute concussion interventions (≤1 month post-injury), non-nutritional therapies, non-peer-reviewed sources, and conference abstracts lacking full data [13].

The initial search results were imported into a reference management system, and duplicates were removed. Two independent reviewers (JF and XW) screened titles and abstracts for eligibility, followed by full-text assessments. Any discrepancies in study inclusion were resolved through discussion, and if consensus could not be reached, a third reviewer adjudicated the decision. This multi-step process ensured methodological rigor and minimized selection bias.

2.3. Data Extraction

Data extraction was performed independently by the same two reviewers using a standardized form. Extracted information included study characteristics (author, year, country, study design), participant demographics (sample size, age, sex), intervention details (type, dosage, duration), comparator types, outcome measures, follow-up duration, and key findings. Outcome measures encompassed cognitive performance tests, sleep quality assessments, mood scales, fatigue evaluation, and functional recovery indices. When necessary, authors of included studies were contacted to obtain missing or clarifying data. The extracted data were cross-checked to ensure accuracy, and disagreements were resolved through discussion to reach consensus.

2.4. Quality Evaluation

The methodological quality of included studies was rigorously evaluated. RCTs were assessed using the Cochrane Risk of Bias 2 (RoB2) tool, which examines domains including randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting [14]. Non-randomized studies were evaluated with the ROBINS-I tool, addressing potential biases due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Assessments were conducted independently by two reviewers, with disagreements resolved by discussion and consensus. Overall risk of bias for each study was categorized as low, moderate, or high, providing a framework to interpret the reliability of study findings.

2.5. Data Synthesis and Analysis

Given the heterogeneity of interventions, study designs, and outcome measures, a narrative synthesis was primarily conducted. Where possible, quantitative data were summarized using descriptive statistics, and effect sizes were reported when provided in the original studies. The synthesis focused on patterns of symptom improvement across cognitive, mood, sleep, and functional domains, highlighting consistencies and divergences in outcomes. Limitations of individual studies, including small sample sizes, short follow-up durations, and methodological constraints, were carefully noted to inform the discussion and future research recommendations.

3. Results and Analysis

3.1. Article Selection and Quality Assessment

Figure 1 illustrates the PRISMA flowchart depicting the study identification, screening, and inclusion process. A total of 674 records were initially retrieved from the electronic databases. After removal of duplicates and screening based on titles and abstracts, 42 full-text articles were assessed for eligibility, of which 9 studies met the predefined inclusion criteria (Table 2). Two studies were excluded due to insufficient sample size or unclear diagnostic criteria [11].

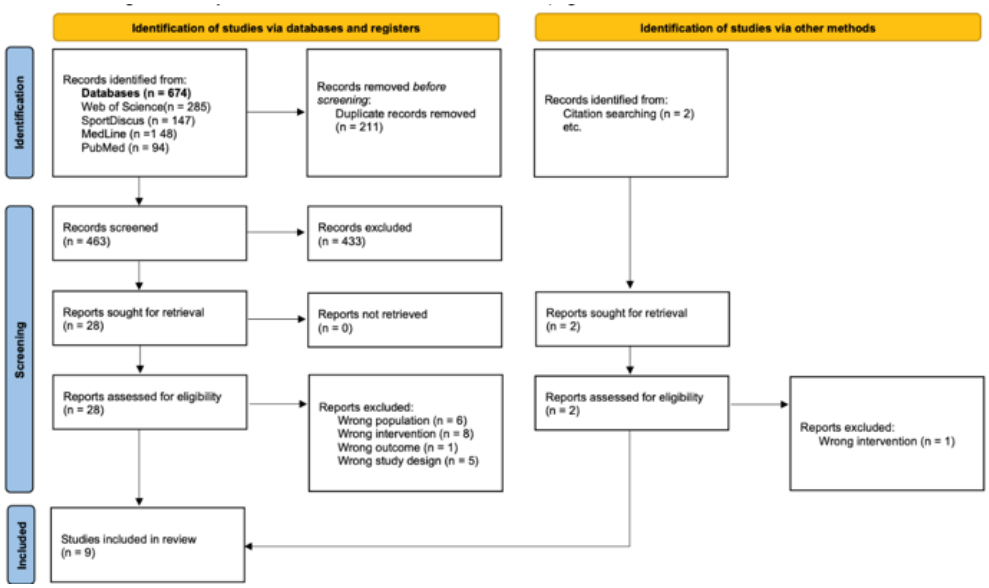

Figure 1. PRISMA flowchart demonstrating study search, screening and inclusion process, in accordance with Page.

Table 2. Characteristics of the Included Studies.

Design	Sample Size / Population	PCS Characteristics
RCT	n=62 (youth, 44% male)	Persistent symptoms 4-6 weeks post-injury
RCT	n=72 (youth, 42% male)	Sleep disturbance after concussion
Cohort study	n=83 (adolescents)	Persistent headaches post-mTBI
RCT	n=99 (youth)	Persistent symptoms >4 weeks
RCT	n=78 (adults, 50% male)	PCS symptoms within 12 months
RCT	n=60 (adults)	PCS symptoms 3-12 months
RCT	n=42 (athletes)	History of sport-related PCS
Pilot study	n=14 (adults)	PCS symptoms, 2-6 months post-injury
Case-control	n=4 (post-menopausal women)	Diagnosed PCS

Among the included studies, the majority were randomized controlled trials (RCTs) published after 2013, with a few cohorts, pilot, or case-control studies. Risk of bias was assessed using the Cochrane RoB2 tool for RCTs and the ROBINS-I tool for non-randomized studies. Approximately 50% of RCTs were judged to be at low risk of bias, while the remaining RCTs were rated as having a moderate risk, mainly due to issues in blinding and incomplete outcome data. Of the three non-randomized studies, two were rated at serious risk of bias, largely attributable to confounding factors and measurement inconsistencies, while one study was assessed as moderate overall. These assessments indicate that while most RCTs provide relatively reliable evidence, caution is warranted when interpreting findings from non-randomized studies.

3.2. Characteristics of Studies and Interventions

All included studies employed standardized scales to assess PCS symptoms, such as the Post-Concussion Symptom Inventory (PCSI) and the Cognitive Failures Questionnaire (CFQ). Primary outcomes were focused on symptom relief, including cognitive function, mood, sleep quality, fatigue, and overall quality of life. Follow-up durations ranged from 1 to 6 months. Four studies involved children or adolescents, while the remaining studies focused on adult populations, including athletes and postmenopausal women. Most studies targeted mild TBI, although some specifically investigated sport-related concussions.

The nutritional interventions evaluated included melatonin, Enzogenol, MLC901, ketogenic diets, and phytocannabinoids (CBD/THC) (Table 3). Key findings are summarized as follows:

- **Melatonin**: Primarily studied in youth populations, melatonin consistently improved sleep quality and demonstrated partial benefits for mood and cognitive function. Neuroimaging evidence in some studies suggested enhanced functional connectivity, although results were not uniformly statistically significant.
- **MLC901**: Administered in adults with PCS, MLC901 showed notable improvements in attention and executive function. However, these cognitive benefits diminished after discontinuation, and no sustained effects were observed for fatigue or overall quality of life.
- **Enzogenol**: Well tolerated across studies, Enzogenol reduced mental fatigue, enhanced sleep quality, and yielded self-reported cognitive improvements. Objective cognitive tests produced mixed results, indicating variability in individual response or sensitivity of measures.
- **Ketogenic diet**: In a small pilot study, adherence to a ketogenic diet significantly improved visual memory and overall PCS symptom scores, with supporting evidence from metabolic biomarker changes. However, the sample size was limited, and findings require validation in larger cohorts.
- **Phytocannabinoids (CBD/THC blends)**: Preliminary evidence suggested improvements in autonomic regulation (heart rate and blood pressure variability) and symptom relief. Nevertheless, the small sample size and high inter-individual variability limited generalizability.

Table 3. Summary of Outcomes Measured and Results.

Intervention	Participants	Main Outcomes	Results
Melatonin	Youth with PPCS	Sleep, PCS symptoms	Improved sleep, enhanced neural connectivity
Melatonin	Youth with PPCS	Sleep, QoL, cognition	Partial improvement; some outcomes not significant
MLC901 capsules	Adults with TBI	Cognition, fatigue, QoL	Improved attention; other outcomes not significant
Enzogenol	Adults with mTBI	Cognition, mood, sleep	Cognitive improvement; mixed results on objective measures
Enzogenol	Collegiate athletes	Sleep, cognition	Reduced fatigue, EEG changes observed
Ketogenic diet	Adults with PCS	Visual memory, PCS symptoms	Significant memory improvement; symptom score reduction
CBD/THC blends	Post-menopausal women with PCS	HRV, BPV, symptoms	Improved autonomic function; reduced PCS symptoms

Overall, despite heterogeneity in study design, population, and outcome measures, nutritional interventions demonstrated promising effects on PCS symptoms, particularly

in cognitive function, sleep quality, and fatigue reduction. However, small sample sizes, short follow-up periods, and varying methodological rigor highlight the need for further high-quality, large-scale studies to confirm these preliminary findings.

4. Finding and Discussion

This systematic review highlights that nutritional interventions can contribute to alleviating a range of PCS symptoms, including cognitive deficits, memory impairments, sleep disturbances, mood disorders such as depression, and fatigue. These interventions appear to offer a promising complement to conventional pharmacological and rehabilitative treatments. However, the heterogeneity of study designs, participant characteristics, and outcome measures leads to variability in reported efficacy, limiting the generalizability of findings.

4.1. Participant and Study Characteristics

Significant limitations were identified in the profiles of study participants. Only Singh et al. specifically targeted postmenopausal women, while most studies either included mixed-gender populations or did not stratify outcomes by sex, leaving potential gender-specific responses largely unexplored. Age groups were often studied in isolation, with few trials directly comparing children, adolescents, and adults, which limits understanding of developmental or age-related differences in PCS recovery and response to nutritional interventions. Moreover, most studies did not adequately control for participants' habitual diets, lifestyle factors, or co-administered medications, introducing potential confounding variables that may have influenced the observed outcomes. Sample sizes were generally small, particularly in pilot or case-control studies, reducing statistical power and the robustness of effect estimates.

4.2. The Possible Role of Nutrition in Recovery from PCS

This review evaluated five primary nutritional interventions-melatonin, Enzogenol, MLC901, ketogenic diet, and phytocannabinoids-highlighting their potential mechanistic and therapeutic roles in PCS management:

- **Melatonin**: Evidence suggests melatonin can improve sleep quality and mood, potentially facilitating cognitive recovery by regulating circadian rhythms and reducing neuroinflammation. Nevertheless, efficacy varied with dose, duration, and study design, and evidence for relief of headaches in pediatric populations was inconsistent. Neuroimaging studies indicate possible enhancements in functional connectivity, though findings require replication.
- **Enzogenol**: Enzogenol supplementation demonstrated modest benefits for reducing mental fatigue and improving self-reported cognition. The mechanisms may involve antioxidant and anti-inflammatory properties that protect neural tissue. However, objective measures often showed mixed results, suggesting that observed effects might partly reflect placebo or subjective reporting biases.
- **Ketogenic diet**: Both human and preclinical studies indicate that ketogenic diets can enhance memory performance and overall PCS symptom profiles, likely by providing neuroprotective ketone bodies and reducing oxidative stress. Despite these benefits, long-term adherence is challenging due to palatability, cost, and individual tolerance, limiting widespread clinical applicability.
- **MLC901**: MLC901 exhibited improvements in attention and executive function, supported by animal studies demonstrating neurogenesis and synaptic plasticity. However, its effects on fatigue, mood, and broader functional outcomes were inconsistent, and evidence for severe TBI populations remains limited. The persistence of benefits post-intervention also appears short-lived.
- **Phytocannabinoids (CBD/THC)**: Preliminary findings suggest potential for improving autonomic regulation, alleviating headaches, and reducing certain PCS

symptoms. However, evidence is constrained by very small sample sizes, heterogeneous dosing protocols, and variable individual responses, underscoring the need for rigorous dose-finding studies.

Taken together, these nutritional interventions suggest a multifaceted therapeutic potential, particularly in enhancing cognitive function, sleep quality, and emotional well-being. They may serve as adjunctive strategies alongside pharmacological therapies, rehabilitation, and lifestyle modifications to support long-term PCS recovery.

4.3. Limitations

Several limitations of the current evidence base must be acknowledged. First, study designs and populations were highly heterogeneous, complicating direct comparison and meta-analytic synthesis. Second, small sample sizes reduced statistical power and increased susceptibility to type II errors. Third, intervention protocols-including dosages, durations, and formulations-were inconsistent, limiting reproducibility. Fourth, many studies relied heavily on subjective outcome measures, such as self-reported questionnaires, which may introduce bias. Lastly, follow-up periods were generally short, providing limited insight into the long-term efficacy and sustainability of nutritional interventions for PCS recovery.

4.4. Future research

To strengthen the evidence base, future research should prioritize large-scale, well-controlled trials with standardized dosing protocols and extended follow-up durations. Integration of objective outcome measures, including neuroimaging, electrophysiology, and metabolic biomarkers, would improve the reliability and interpretability of results. Exploring individualized treatment protocols based on patient characteristics-such as age, sex, baseline diet, and genetic predispositions-may enhance efficacy and reduce variability. Furthermore, studies should consider combinatory approaches that integrate nutritional, pharmacological, and behavioral interventions to assess potential synergistic effects. Rigorous long-term studies will be essential to translate these preliminary findings into evidence-based clinical guidelines for PCS management.

5. Conclusion

This systematic review comprehensively evaluated the therapeutic potential of nutritional interventions in the management of post-concussion syndrome (PCS). Among the five interventions studied-melatonin, Enzogenol, MLC901, ketogenic diets, and phytocannabinoids-evidence suggests they may improve key domains affected by PCS, including cognitive function, memory, mood disturbances, sleep quality, and fatigue. These interventions were generally well tolerated and demonstrated a favorable safety profile, highlighting their potential as complementary strategies alongside conventional pharmacological and rehabilitative therapies.

Mechanistically, these nutritional approaches may exert their effects through modulation of neuroinflammation, reduction of oxidative stress, enhancement of neuronal plasticity, and support for nerve repair and functional connectivity. However, the current evidence base is limited by several factors, including small sample sizes, heterogeneity in participant demographics, short follow-up durations, reliance on subjective outcome measures, and variability in intervention protocols. These limitations constrain the generalizability and robustness of conclusions.

Future research should focus on large-scale, rigorously controlled trials with standardized intervention protocols, including well-defined dosages, administration schedules, and longer-term follow-up to assess sustained effects. Incorporating objective biomarkers, neuroimaging, and functional assessments will further elucidate underlying mechanisms and validate efficacy. Additionally, exploration of individualized treatment

strategies tailored to patient characteristics such as age, sex, injury severity, and baseline nutritional status could optimize therapeutic outcomes.

In summary, nutritional interventions represent a promising adjunctive approach for PCS rehabilitation, with the potential to improve patient outcomes, enhance quality of life, and reduce the overall healthcare burden associated with long-term post-concussion sequelae. With further high-quality research, these strategies may be integrated into evidence-based clinical guidelines, offering a safe, accessible, and effective complement to current PCS management practices.

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