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Review Article

Dietary supplementation roles in concussion management: A systematic review

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Abstract

Concussion, one of the most common types of mild traumatic brain injury, remains a global problem that poses substantial effects on individuals, families, and society. When dealing with concussion, clinicians primarily focus on symptomatic treatment and modified activity with no established therapies specifically addressing the underlying pathophysiological changes. In recent years, there has been a growing increase in attention to the effectiveness of dietary supplements (DS) and nutritional interventions as adjunctive therapy options for concussion. Hence, this review aims to comprehensively explore the existing human studies on using DS as adjunctive therapy in the management of concussion. This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The search strategy was created based on the population, intervention, comparison, outcome framework. The findings are conveyed narratively and analyzed according to the timing of the intervention. DS administered within 7 days of onset were classified as acute interventions, while those given after this period were classified as nonacute interventions. After screening, we identified 21 reports for 19 studies involving 13 DS. Thirteen DS were included in this review. Notably, omega-3 polyunsaturated fatty acids were the most extensively studied and accounted for 23.81% of studies, followed by melatonin and pine bark extract (19.05% and 9.5%). At least 13 supplements were identified in clinical studies, with 77% demonstrating favorable outcomes. However, none of the interventions reviewed offer strong enough evidence to justify regular use in clinical practice.

Keywords: *Concussions, Supplementations, Traumatic brain injury*

Introduction

Concussion, one of the most common types of mild traumatic brain injury (mTBI), remains a global problem that poses substantial effects on individuals, families, and society [1]. In the United States, at least 24% of adolescents reported one concussion during their lifetime [2]. Even so, the actual incidence of concussions remains uncertain, as a significant number of individuals sustaining concussions do not seek medical care [3]. Concussions typically result in temporary neurologic dysfunction, such as headache, dizziness, light-headedness, and cognitive impairment, which usually resolve within minutes to hours [4]. However, despite being commonly regarded as "mild," approximately 10%–20% of concussion patients developed persistent disabilities associated with pathological changes of the brain that significantly affect the quality of life [5,6].

The pathophysiology of concussion encompasses complex mechanisms triggered by initial biomechanical impact. These processes include axonal stretching, ionic imbalance, oxidative stress, and neuroinflammation that lead to energy depletion, altered neurotransmission, and increased vulnerability to future injuries [7,8]. These issues are especially more concerning in individuals frequently subjected to repetitive head impacts, such as athletes and military personnel, who are at risk for progressive neurodegenerative changes [9,10].

When dealing with concussion, clinicians primarily focus on symptomatic treatment and modified activity with no

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established therapies specifically addressing the underlying pathophysiological changes [11,12]. In recent years, there has been a growing increase in attention to the effectiveness of dietary supplements (DS) and nutritional interventions as adjunctive therapy options for concussion [13,14]. Preclinical studies have demonstrated the potential efficacy of various DS, including creatine [15], curcumin [16], Vitamin D, and omega-3 polyunsaturated fatty acids (ω3-PUFA) [17], in managing TBI. These compounds have beneficial effects by regulating neuroinflammation and oxidative stress, which are essential pathophysiological changes frequently observed after a concussion. Several clinical studies support the findings in the preclinical studies, yet a significant gap in translating them into daily practice remains [11,18,19]. Hence, this review aims to comprehensively explore the existing human studies on using DS as adjunctive therapy in the management of concussion. By analysing the effectiveness, safety, and pathogenesis, we hope to increase understanding of their value in concussion management and provide guidance for further research.

Methods

Search strategy

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [20]. The search strategy was created based on the population, intervention, comparison, and outcome framework. The "Population" term included modification of "mild head injury" OR "concussion" OR "postconcussive." The "intervention" term encompassed modified "dietary supplement" terms. Specifically, we included natural compounds that had potential as concussion treatment, such as ω3-PUFA, curcumin, resveratrol, creatine, green tea, caffeine, Vitamin E, Vitamin C, and Vitamin D [18]. We included all reported outcomes, including clinical assessments, radiological findings, brainwave activity, and biomarkers. Literature searching was conducted in several databases, including PubMed, Scopus, and Web of Science, enrolling all literature published from inception to July 2024. It is important to note that the terms mTBI and concussion were used interchangeably throughout this review [21].

Eligibility criteria

The inclusion criteria were (1) research conducted on human subjects, (2) a clear distinction of mTBI population in the study, (3) a clear type of DS intervention, (4) assessing either at least one concussion symptom or markers correlated with a concussion, and (5) written in English. Animal studies, case reports, case series, and studies that included obvious abnormalities in CT scans or MR imaging were excluded. Conference abstracts, guidelines, consensus statements, reviews, and meta-analyses were also excluded.

Selection and data collection processes

The search term was developed after consultation with the librarian to ensure comprehensive coverage. After removing the duplications, one author conducted an initial screening of the titles and abstracts based on inclusion/exclusion criteria. Potential full texts based on title/abstract screening were obtained and reviewed independently by two authors. Any disagreement during the review process were resolved throughout discussion with the third and fourth authors. In addition, two authors screened relevant reviews published in the last 5 years. Then, two authors extracted the required data to carry out this review.

Data extraction

Extracted data from included studies were study design, diagnostic criteria of concussion or mTBI, number of participants, age of participants, details of the intervention (type, dosage, and duration), time interval from the occurrence of mTBI to intervention, and outcome. Outcomes reported in this review were clinical and markers. Clinical outcomes were depression, mental, cognition, memory, pain, and sleep. When multiple clinical outcomes were reported, they will be classified as either global or postconcussion syndrome. Biomarkers analyzed as outcomes included serum injury markers, magnetic resonance imaging findings, and electroencephalography results. Data were analyzed using Microsoft Excel (Microsoft Corp).

Quality assessment

The modified Black and Downs quality rating tool was used to assess the quality of the included studies [22]. This tool assesses five domains: study quality, external validity, internal validity and bias, confounding and selection bias, and the study's power, with a maximum score of 28. Based on the sum of the scores, studies are classified into poor (≤14), fair (15–19), good (20–25), and excellent (26–28).

Synthesis of the result

Due to the diverse dietary regiments, various causes of concussion, diagnostic criteria, and outcomes assessed, combining the quantitative data for a meta-analysis was not feasible. Hence, the findings are conveyed narratively and analyzed according to the timing of the intervention. DS administered within 7 days of onset were classified as acute interventions, while those given after this period were classified as nonacute interventions. If a DS was administered regularly in a period of time to prevent concussion in high-risk subjects, it was classified as a preventive measure. We also categorized the included reports based on age, encompassing pediatric and adult populations.

Results

Characteristics of studies and subjects

After screening [Figure 1], we identified 21 reports for 19 studies involving 13 DS. Three reports were derived from a single study that assessed the same subjects but examined different outcome measures. In total, this review comprised 6336 participants, including 1261 in the DS group and 5075 being part of control groups. This review included 11 randomized controlled trials (RCTs), five pilot studies, one prospective controlled study, two prospective studies without control groups, and one retrospective study. Characteristics of included studies can be reviewed in Supplementary Table 1. Approximately 19.05% of the included studies were multicenter, with over half conducted in the United States. The quality assessment revealed that only 14.29% of the studies were rated as good, 42.86% as fair, and 42.86% as poor

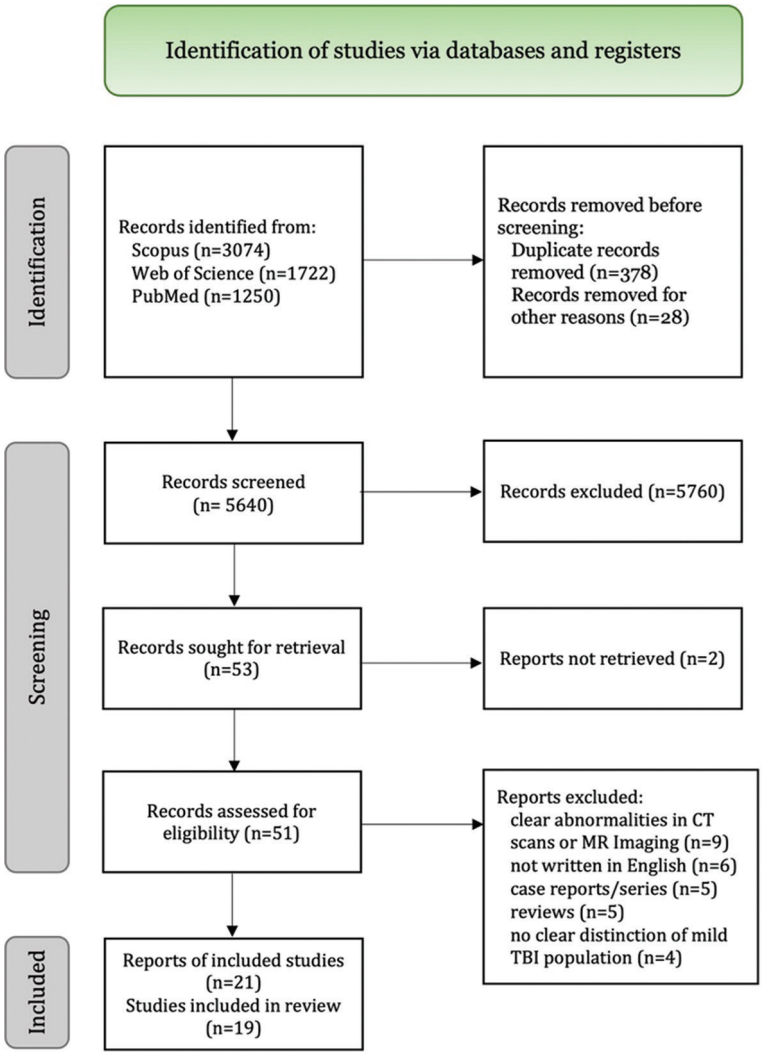

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of included studies

[Figure 2]. Detailed quality assessment reports are available in Supplementary Figure 1.

The majority of the reported causes of concussion (72.24%) were not specific, with 19.03% related to sports injuries, and 8.72% to combat-related injuries. Among sport-related injuries, American football was the most commonly evaluated. The included studies varied in their focus on the timing of intervention. Six studies were conducted in an acute setting, eight in a nonacute setting, and five studies assessed dietary supplementation as a preventive measure. Across the included research, ten distinct diagnostic criteria were employed, mostly the American Academy of Neurology Criteria, International Conference of Concussion criteria, and Sport Concussion Assessment Tool 5 [Figure 3].

Dietary supplements evaluated

Thirteen DS were included in this review. Notably, ω3-PUFA acids were the most extensively studied, accounted for 23.81% of studies, followed by melatonin and pine bark extract (19.05% and 9.5%). However, based on the number of subjects involved [Figure 4], cerebrolysin emerged as the most extensively studied DS, accounting for 59.08% of subjects included in this review, based on a large multi-center retrospective study [23], followed by ω3-PUFA (10.86%) and melatonin (8.01%) [Figure 5].

Dietary supplements in acute settings

Pediatrics

Two DS (Docosahexaenoic acid [DHA] - and magnesium oxide) were evaluated in acute pediatric settings. Miller *et al*. conducted an RCT administering 2 g of DHA daily for 12 weeks to adolescent athletes with sport-related concussions within 4 days after onset. Participants receiving DHA experienced symptom relief approximately 5 days earlier than the placebo group (11.0 vs. 16.0 days, P = 0.08), with 5% reporting eructation as a side effect [24]. Standiford *et al*. administered 400 mg magnesium oxide twice daily for 5 days to all concussion patients, regardless of the cause, that occurred within 48 h. This intervention resulted in a significant reduction in the PostConcussion Symptoms Scale score at 48 h (P = 0.016) compared to placebo, with no side effects noted [25].

Adults

In adult subjects, four DS – N-acetylcsyteine (NAC),

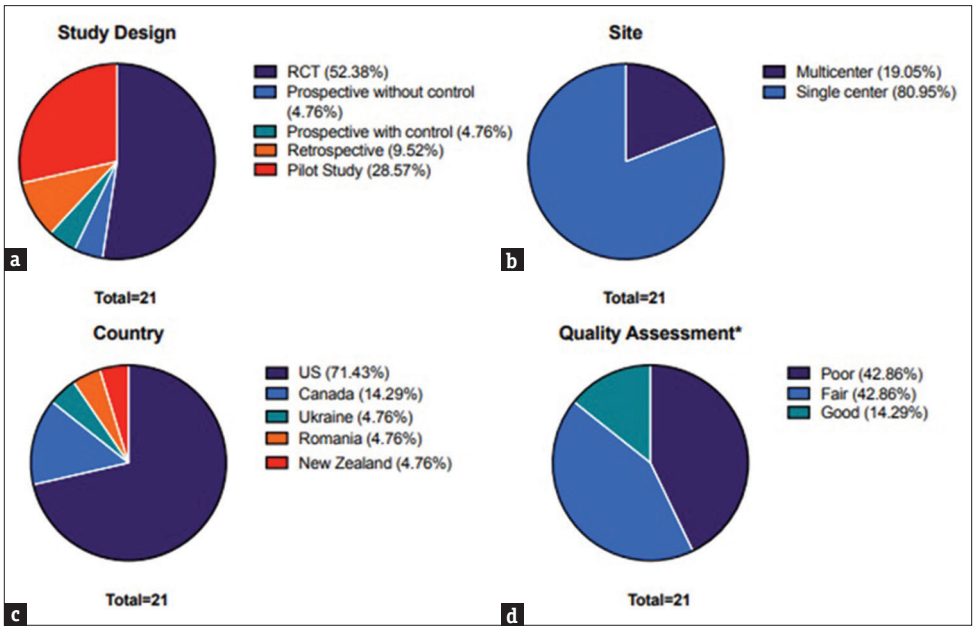

Figure 2: Characteristics of the Included Studies. The majority of the studies included in this review were randomized controlled trials (a), with 28.5% classified as pilot studies. Most of the research was conducted at single-center (b) in the United States (c). However, no study was categorized as excellent according to the quality assessment criteria. The majority of the studies received ratings of poor or fair (d). RCT: Randomized Controlled Trial

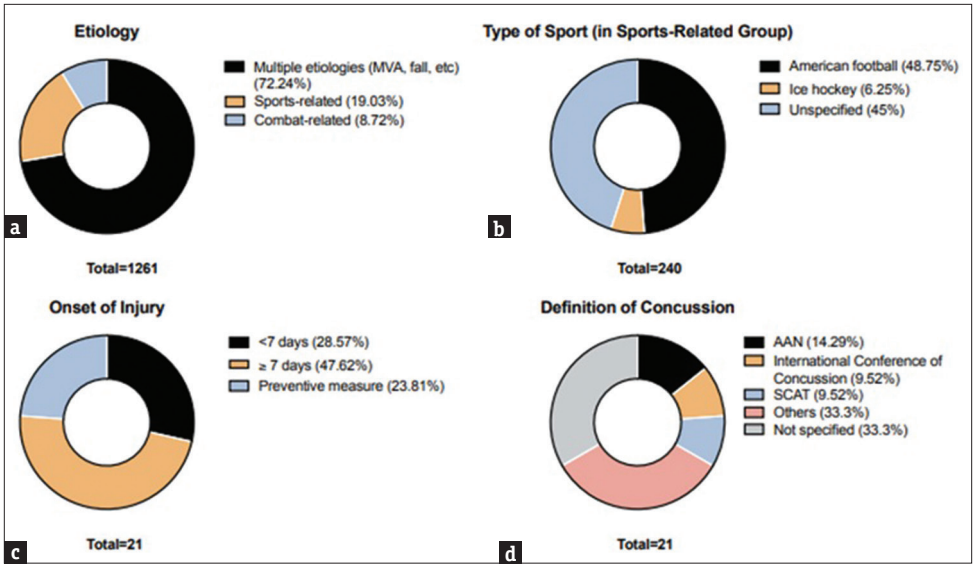

Figure 3: Characteristics of the Subjects. In the majority of the studies included, the etiology was not specified. Among all studies, 19.03% focused on sport-related injuries (a). Within the category of sport-related injuries, American football was the most extensively researched sport (b). Less than one-third of the included studies were conducted in acute injury settings, defined as occurring within less than seven days (c). The criteria utilized varied across the studies, with the American Academy of Neurology (AAN), the International Conference on Concussion, and the Sport Concussion Assessment Tool (SCAT) being employed in most of the investigations (d).

branched-chain amino acids (BCAA), riboflavin, and cerebrolysin – were explored. Kent *et al*. reported that 400 mg of daily riboflavin for 2 weeks reduced recovery time in sport-related concussions occurred within 24 h (9.92 days vs. 22.2 days for placebo, $P < 0.05$) with no adverse effects [26]. Hoffer *et al*. gave 4 g of daily intravenous NAC for 7 days in an RCT involving subjects with combat-related concussion, noting that early administration (within 24 h) correlated with improved outcomes in 86% of subjects compared to only 42% in subjects treated later (26–72 h after impact). Notably, no side effects were reported in this study [27]. Corwin *et al.* explored the effect of BCAA in concussions that occurred within 72 h and found significant reductions in total symptom scores (decrease of 4.4 points [$P = 0.0036$]) and faster return to baseline activity (increase of 0.503 points [$P = 0.0053$]) with gastrointestinal side effects in the high-dose group [28]. A large retrospective study conducted by Muresanu *et al*. ($n = 5,532$), indicated that 20–30 mL/day of cerebrolysin for 10 days improved Glasgow Outcome Scale scores on day 10 for patients with mild head injuries compared to control but showed no difference by day 30. Diarrhea occurred in <2% of participants [23].

Dietary supplements in non-acute settings

Pediatrics

Melatonin was the only DS assessed in pediatric nonaccute settings. In the initial report, Barlow *et al*. reported that administering either 3 or 10 mg of melatonin for 28 days in pediatric patients with a concussion occurring 4–6 months prior resulted in no difference in concussion symptoms resolution compared to control [29]. However, on the subsequent analysis, they reported significant reductions in sleep-related issues score in the 3 mg group (3.7 vs. 7.4 in placebo) and increased of sleep duration compared to placebo (43 min in the 3 mg group and 55 min in the 10 mg group) [30]. Based on the same subjects, Iyer reported positive effects of melatonin on brain connectivity and gray matter volume in the posterior cingulate cortex, resulted in reduced wake periods after sleep ($r = -0.27$, $P = 0.01$), and improved sleep symptoms ($r = 0.29$, $P = 0.02$). Various adverse effects, including fatigue, cognitive problems, nausea, behavioral changes, and insomnia, were reported to occur in 14% of subjects [31]. In contrast, Howell *et al.* found no relation between melatonin use and symptom recovery, although the study lacked control and detailed information on dosage and duration [32].

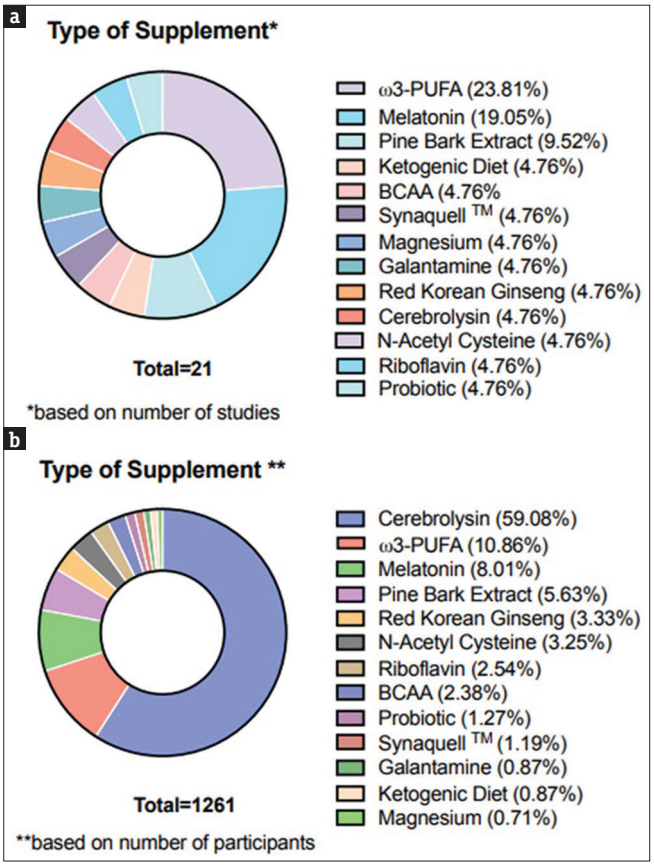

Figure 4: Dietary Supplements Included. Based on the number of studies, omega-3 polyunsaturated fatty acids (ω3-PUFA) were the most extensively explored, comprising 23.81% of the total, followed by melatonin at 19.05% and pine bark extract at 9.52%. The remaining dietary supplements were investigated in only one study each (a). In terms of the number of participants, cerebrolysin was the most extensively studied, accounting for 59.08% of the total participants, followed by ω3-PUFA and melatonin (b). ω3-PUFA: Omega-3 polyunsaturated fatty acids; BCAA: Branched-chain amino acids

Adults

Six studies utilized five DS on adults (probiotics, ketogenic diet, pine bark extract, galantamine, and red Korean ginseng) in nonacute settings. Theadom *et al.* and Walter *et al*. both found that pine bark extract significantly improved cognitive failures and neurocognitive symptoms in individuals with persistent postconcussive symptoms. Several adverse effects, such as headache and sleep disturbance, were noted [33,34]. Korshnyak *et al*. reported amelioration of symptoms related to the vegetative nervous system after administration of Red Korean Ginseng in a prospective study involving subjects who experienced combat-related concussion within 4–6 years. No adverse effects were reported; however, this study lacked a control group [35].

On the other hand, a pilot study investigating probiotics [36], ketogenic diets [37], and galantamine [38] failed to show significant improvements in symptoms.

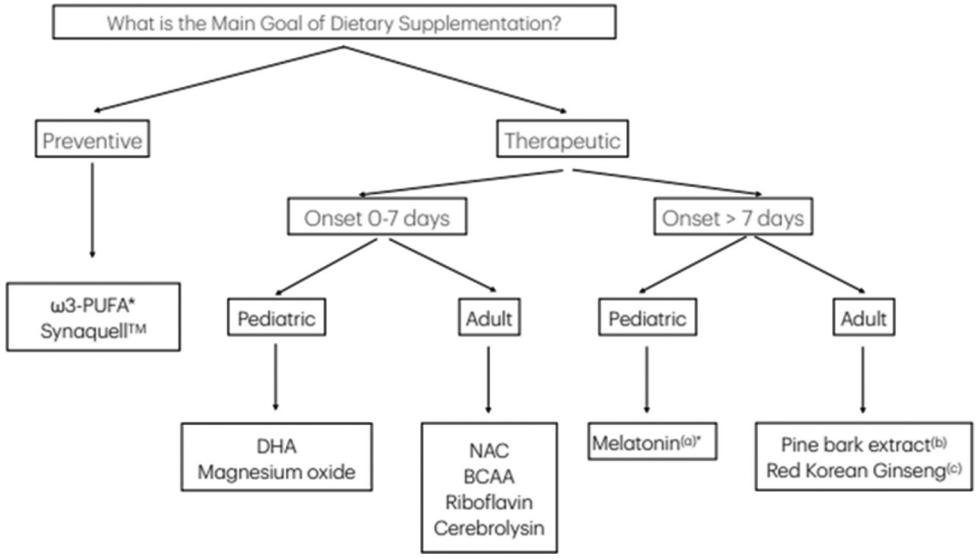

Figure 5: Potency of dietary supplements as adjunctive therapy in concussion

Brenner *et al.* found that daily probiotic supplementation for 8–10 weeks in subjects with persistent postconcussive symptoms did not improve social stress test scores compared to placebo, although a decrease in plasma C-reactive protein concentrations was noted, with no adverse effects reported [36]. In another pilot study, McAllister *et al*. assessed galantamine over a 14-week period and found no noticeable improvement of cognitive complaints or other symptoms, but noting adverse effects in seven subjects (63%) [38]. Similarly, Rippee *et al.* found no significant improvement in cognitive or concussive symptoms among those following a ketogenic diet, with some participants experiencing adverse effects including diarrhea and fatigue [37].

Preventive measure

This review identified five studies involving 210 participants that focused on preventing concussions through dietary supplementation. All studies targeted young amateur athletes – four focused on American football and one on amateur ice hockey players. Among all, ω3-PUFA, particularly DHA, eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA), emerged as the most extensively studied supplements, present in four studies involving 188 participants in total.

In 2016, Oliver *et al*. administered varying doses of DHA (2, 4, and 6 g) from the preseason throughout the sports season for 27 weeks. Their findings indicated decreases in neurofilament-light protein levels across all dosage groups [39]. Heileson *et al.* further confirmed these findings with a daily dosage of a combination of DHA, EPA, and DPA in a total dose of 2.9 g from preseason through the end of the season, correlating similar decrease in neurofilament levels observed [40]. However, Mullins *et al*. did not observe changes in neurofilament levels with 3.5 g of DHA and EPA administered five times weekly, although they noted a significant correlation between increased concentrations of these fatty acids and reduced neurofilament levels in the blood [41]. Furthermore, Mullins *et al*. showed that ω3-PUFA supplementation throughout the competitive season increased circulating levels of phosphatidylcholine species that contain DHA and EPA [42]. While common side effects included gastrointestinal discomfort (reported in 8 cases), halitosis (in 5 cases), and mild instances of acne (2 cases) were associated with ω3-PUFA, no severe adverse effects were reported.

Breuer *et al.* examined SynaQuell™, a commercially available supplement comprising ketones, BCAA, coenzyme Q10, DHA, and nicotinamide riboside. A daily dosage of 7.7 g was administered to amateur ice hockey players over 84–112 days, starting midseason. Participants in the SynaQuell™ group demonstrated significant improvements in neurocognitive function, along with reductions in neurofilament concentrations, indicating the potential of this supplement in concussion prevention. Notably, no adverse effects were documented during this study [43].

Adverse effects observed across studies

The most frequently reported adverse effects across the studies were gastrointestinal symptoms, including eructation, bloating, abdominal discomfort, and diarrhea. These gastrointestinal issues were particularly noted in studies involving DHA, high-dose BCAA, cerebrolysin, probiotics, ketogenic diet, and ω3-PUFA. In comparison, melatonin exhibited the highest incidence of side effects, with fatigue and cognitive difficulties reported in up to 14% of participants; however, it is important to note that these effects did not significantly differ from those observed in the placebo group [29]. Notably, no adverse events were documented in studies utilizing riboflavin, NAC, magnesium oxide, red Korean ginseng, or SynaQuell™.

Discussion

This systematic review evaluated the role of DS in the management and prevention of concussions. We identified at least 13 supplements documented in clinical studies, with positive outcomes associated with 77% of the supplements examined. However, no intervention included in this review provided sufficient evidence to warrant regular use in clinical practice. Nonetheless, our findings underscore the potential of DS as an adjunctive treatment in concussion management [Figure 5].

Efficacy of dietary supplements

While robust evidence supporting the efficacy of DS was lacking, the review provides insights into their potential benefits for concussion management [Figure 6]. Among the various supplements, ω3-PUFA emerged as the most extensively studied and demonstrated effectiveness in both acute settings and as a preventive measure. It is important to note, however, that studies assessing ω3-PUFA as preventive measures predominantly focused on serum neurofilament-light chain protein (Nf-L) as an outcome, rather than clinical symptoms. Serum neurofilament-light chain protein is recognized as a promising biomarker for concussion management [44]. However, several factors, including body mass index and age, may influence Nf-L concentrations, complicating its utility in clinical assessment [45]. Furthermore, the Nf-L profile in individuals with postconcussion syndrome remains conflicting [46,47]. Despite these limitations, the minimal adverse effects associated with ω3-PUFA supplementation suggest that its use as a preventive measure in populations at high risk for sport-related concussions may be justified.

Sleep problems commonly occur in individuals with postconcussion syndrome and are related to prolonged recovery [48,49]. Melatonin is crucial in regulating the sleep–wake cycle, and studies have shown a reduction in endogenous evening melatonin following TBI [50,51]. In children with postconcussion syndrome, melatonin has been found to effectively increase sleep duration, reduce sleep-related issues, and affect brain connectivity. However, it is worth noting that no difference in general symptom resolution compared to the placebo group, raising questions about the efficacy of this supplement in managing concussion. Several adverse effects, such as insomnia and fatigue, were reported after melatonin administration. Importantly, it is important to note that these adverse effects resemble the symptoms of postconcussion syndrome itself [29]. While melatonin should be used with

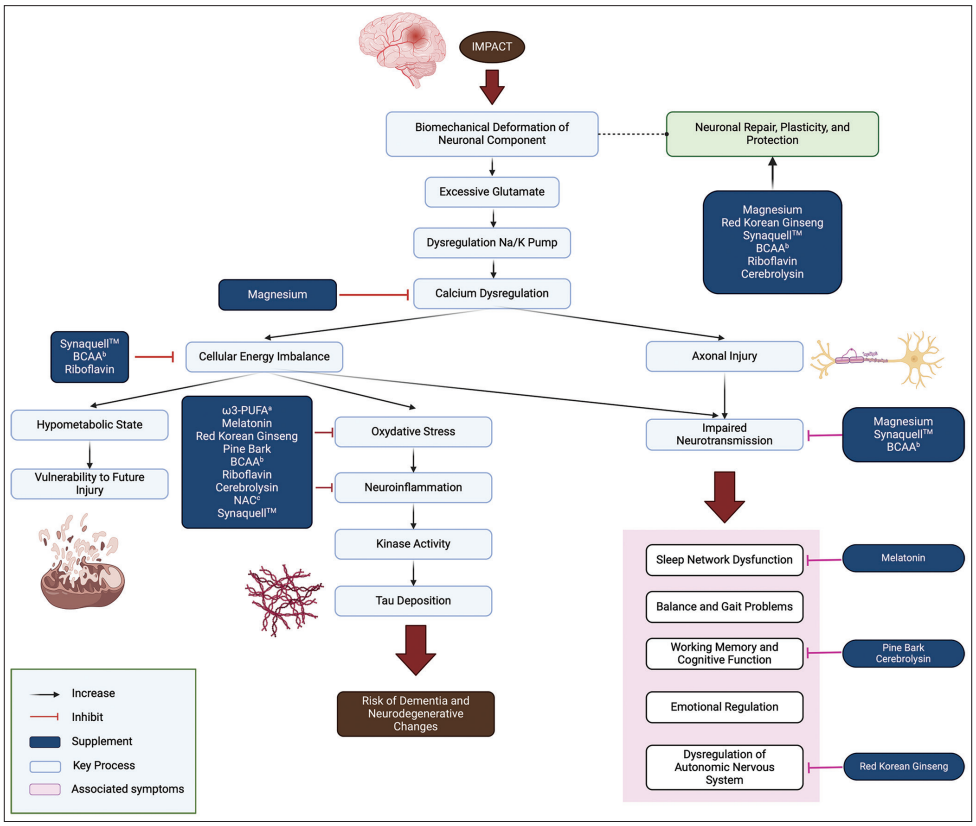

Figure 6: Possible mechanisms of action of dietary supplements in concussion

caution, especially in children, it is commonly not associated with serious adverse reactions, making it a reasonable option for children with sleep problems after concussion [52]. Some authors proposed the benefit of melatonin on adult TBI in general [53]; however, more research is needed to clarify its role in managing concussion specifically in adult populations.

Magnesium, BCAA, riboflavin, NAC, cerebrolysin, and red Korean ginseng are reported to have a statistically significant positive impact on concussion but only assessed in one study for each supplement. Translating this limited evidence into clinical practice must be conducted with caution. However, it is important to note that none of these DS were associated with serious adverse effects. Even this finding aligns with the prevailing assumption regarding the relative safety of DS, a study estimated that there are more than 20,000 annual visits to the ED related to the adverse effects of DS in the US [54]. This estimation may not accurately reflect the true incidence and could be undervalued or overvalued, as clinicians may have less knowledge of the adverse effects of DS in comparison to recognized adverse effects of known pharmaceutical substances [55]. Further research regarding the adverse effects of DS is crucial.

It is widely acknowledged that early management of TBI, including concussion, is linked to a more rapid recovery and improved outcome [56,57]. Interestingly, only one study has particularly investigated the correlation between the timing of intervention and patient outcomes. The study revealed that initiating the intervention at an earlier stage resulted in improved outcomes [27]. Even though our narrative analysis primarily focused on the timing of intervention [as described in Figure 5], we believe that the window of possibility of the use of DS across the provided evidence is still available, considering that concussion is a dynamic change, especially among high-risk groups such as contact sport athlete and military personnel. Chronic progressive neuroinflammation was observed up to several months following impact and was related to functional impairment [58-60]. Additional research is substantially needed to delineate the optimal timing and duration for DS intervention in concussion.

Mechanism of action

We found that no study has specifically assessed the potential explanation for the positive effects of DS in managing concussion. Given the pathogenesis of concussion is highly complex and heterogeneous, encompassing alteration at both cellular and systemic levels [61], substances with multiple sites of action, such as DS, may prove beneficial [62,63]. Insights into possible mechanisms underlying these positive effects are provided by several animal studies [64-69]. All DS included in this report exhibit multiple sites of action, with more than half of DS demonstrating anti-inflammatory and antioxidant properties. However, it is important to note that while several DS share anti-inflammatory and antioxidant properties, the clinical benefits based on symptoms vary, thereby highlighting the need for further studies [Figure 6].

Study strengths and limitations

Our study had several strengths. We were able to create a proper review with time-based and goal-based treatment.

We were also able to found several interventions specialized in adult or pediatric populations thus creating a structured review applicable for clinicians. However, our study did have limitations. First, we failed to create meta-analysis comparing control treatment with DS which weakens our level of evidence. This was not possible at the current time being due to the heterogeneous nature. Second, we performed a big-tent review which could exacerbate the heterogenous nature of the data. Further studies should pinpoint specific DS to synthesized a much more appropriate treatment. Third, most studies had the risk of bias. Further study in this area should be performed in accordance with research guidelines to provide a stronger conclusion. Fourth, there is no proper definition of supplementations as of yet. This was applied differently through different studies with different countries. Applicable and proper definitions must be established and applied uniformly to produce a tangible result.

Conclusion

At least 13 supplements were identified in clinical studies, with 77% demonstrating favorable outcomes. However, none of the interventions reviewed offer strong enough evidence to justify regular use in clinical practice. The data were inconsistent, and the risk of bias remains considerable. Still, our results emphasize the possible value of DS as supportive treatments for concussion management.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. All data were available in the respective article included in this systematic review. A summary of the included data can be reviewed in Supplementary Table 1 and Supplementary Figure 1.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Maas AI, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: Progress and challenges in prevention, clinical care, and research. Lancet Neurol 2022;21:1004-60.
2. Veliz P, McCabe SE, Eckner JT, Schulenberg JE. Trends in the prevalence of concussion reported by US adolescents, 2016-2020. JAMA 2021;325:1789-91.
3. Schmidt JD, Broglio SP, Knight K, Leeds D, Lynall RC, D'Lauro C, et al. Optimizing concussion care seeking: A longitudinal analysis of recovery. Am J Sports Med 2023;51:214-24.
4. Hallock H, Mantwill M, Vajkoczy P, Wolfarth B, Reinsberger C, Lampit A, et al. Sport-related concussion: A cognitive perspective. Neurol Clin Pract 2023;13:e200123.
5. Taskina D, Zhu C, Schwab N, Hazrati LN. Brain pathology and symptoms linked to concussion history: Beyond chronic traumatic encephalopathy. Brain Commun 2024;6:fcad314.
6. Churchill NW, Hutchison MG, Graham SJ, Schweizer TA. Acute and chronic effects of multiple concussions on midline brain structures. Neurology 2021;97:e1170-81.
7. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. Neurosurgery 2014;75(Suppl 4):S24-33.
8. Romeu-Mejia R, Giza CC, Goldman JT. Concussion pathophysiology and injury biomechanics. Curr Rev Musculoskelet Med 2019;12:105-16.
9. Davis GA, Castellani RJ, McCrory P. Neurodegeneration and sport. Neurosurgery 2015;76:643-55.
10. Kim SY, Yeh PH, Ollinger JM, Morris HD, Hood MN, Ho VB, et al. Military-related mild traumatic brain injury: Clinical characteristics, advanced neuroimaging, and molecular mechanisms. Transl Psychiatry 2023;13:289.
11. Hanalioglu D, Hanalioglu S, Arango JI, Adelson PD. Current evidence for pharmacological management of pediatric concussion: A systematic review. Childs Nerv Syst 2023;39:1831-49.
12. Schneider KJ, Leddy JJ, Guskiewicz KM, Seifert T, McCrea M, Silverberg ND, et al. Rest and treatment/rehabilitation following sport-related concussion: A systematic review. Br J Sports Med 2017;51:930-4.
13. Walrand S, Gaulmin R, Aubin R, Sapin V, Coste A, Abbot M. Nutritional factors in sport-related concussion. Neurochirurgie 2021;67:255-8.
14. Feinberg C, Dickerson Mayes K, Jarvis RC 3rd, Carr C, Mannix R. Nutritional supplement and dietary interventions as a prophylaxis or treatment of sub-concussive repetitive head impact and mild traumatic brain injury: A systematic review. J Neurotrauma 2023;40:1557-66.
15. Ainsley Dean PJ, Arikan G, Opitz B, Sterr A. Potential for use of creatine supplementation following mild traumatic brain injury. Concussion 2017;2:CNC34.
16. Khayatan D, Razavi SM, Arab ZN, Niknejad AH, Nouri K, Momtaz S, et al. Protective effects of curcumin against traumatic brain injury. Biomed Pharmacother 2022;154:113621.
17. Scrimgeour AG, Condlin ML, Loban A, DeMar JC. Omega-3 fatty acids and Vitamin D decrease plasma T-Tau, GFAP, and UCH-L1 in experimental traumatic brain injury. Front Nutr 2021;8:685220.
18. Petraglia AL, Winkler EA, Bailes JE. Stuck at the bench: Potential natural neuroprotective compounds for concussion. Surg Neurol Int 2011;2:146.
19. Silverberg ND, Iaccarino MA, Panenka WJ, Iverson GL, McCulloch KL, Dams-O'Connor K, et al. Management of concussion and mild traumatic brain injury: A synthesis of practice guidelines. Arch Phys Med Rehabil 2020;101:382-93.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Syst Rev 2021;10:89.
21. Smith R, Chepisheva M, Cronin T, Seemungal BM. Diagnostic approaches techniques in concussion/mild traumatic brain injury: Where are we? In: Neurosensory disorders in mild traumatic brain injury. Academic Press; 2019, p.247-77.
22. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377-84.
23. Muresanu DF, Ciurea AV, Gorgan RM, Gheorghita E, Florian SI, Stan H, et al. A retrospective, multi-center cohort study evaluating the severity- related effects of cerebrolysin treatment on clinical outcomes in traumatic brain injury. CNS Neurol Disord Drug Targets 2015;14:587-99.
24. Miller SM, Zynda AJ, Sabatino MJ, Jo C, Ellis HB, Dimeff RJ. A pilot randomized controlled trial of docosahexaenoic acid for the treatment of sport-related concussion in adolescents. Clin Pediatr (Phila) 2022;61:785-94.
25. Standiford L, O'Daniel M, Hysell M, Trigger C. A randomized cohort study of the efficacy of PO magnesium in the treatment of acute concussions in adolescents. Am J Emerg Med 2021;44:419-22.
26. Kent JB, Diduch BK, Statuta SM, Pugh K, MacKnight JM. The impact of riboflavin on the duration of sport-related concussion: A randomized placebo-controlled trial. Journal of Concussion 2023;7.
27. Hoffer ME, Balaban C, Slade MD, Tsao JW, Hoffer B. Amelioration of acute sequelae of blast induced mild traumatic brain injury by N-acetyl cysteine: A double-blind, placebo controlled study. PLoS One 2013;8:e54163.

28. Corwin DJ, Myers SR, Arbogast KB, Lim MM, Elliott JE, Metzger KB, et al. Head injury treatment with healthy and advanced dietary supplements: A pilot randomized controlled trial of the tolerability, safety, and efficacy of branched chain amino acids in the treatment of concussion in adolescents and young adults. J Neurotrauma 2024;41:1299-309.
29. Barlow KM, Brooks BL, Esser MJ, Kirton A, Mikrogianakis A, Zemek RL, et al. Efficacy of melatonin in children with postconcussive symptoms: A randomized clinical trial. Pediatrics 2020;145:e20192812.
30. Barlow KM, Kirk V, Brooks B, Esser MJ, Yeates KO, Zemek R, et al. Efficacy of melatonin for sleep disturbance in children with persistent post-concussion symptoms: Secondary analysis of a randomized controlled trial. J Neurotrauma 2021;38:950-9.
31. Iyer KK, Zalesky A, Cocchi L, Barlow KM. Neural correlates of sleep recovery following melatonin treatment for pediatric concussion: A randomized controlled trial. J Neurotrauma 2020;37:2647-55.
32. Howell DR, Potter MN, Provance AJ, Wilson PE, Kirkwood MW, Wilson JC. Sleep problems and melatonin prescription after concussion among youth athletes. Clin J Sport Med 2021;31:475-80.
33. Theadom A, Mahon S, Barker-Collo S, McPherson K, Rush E, Vandal AC, et al. Enzogenol for cognitive functioning in traumatic brain injury: A pilot placebo-controlled RCT. Eur J Neurol 2013;20:1135-44.
34. Walter A, Finelli K, Bai X, Arnett P, Bream T, Seidenberg P, et al. Effect of enzogenol® supplementation on cognitive, executive, and vestibular/balance functioning in chronic phase of concussion. Dev Neuropsychol 2017;42:93-103.
35. Korshnyak VO, Pulyk OR, Stoyanov OM. Rehabilitation of patients with long-term aftereffects of mild combat traumatic brain injury. Wiad Lek 2022;75:300-3.
36. Brenner LA, Forster JE, Stearns-Yoder KA, Stamper CE, Hoisington AJ, Brostow DP, et al. Evaluation of an immunomodulatory probiotic intervention for veterans with co-occurring mild traumatic brain injury and posttraumatic stress disorder: A pilot study. Front Neurol 2020;11:1015.
37. Rippee MA, Chen J, Taylor MK. The ketogenic diet in the treatment of post-concussion syndrome – A feasibility study. Front Nutr 2020;7:160.
38. McAllister TW, Zafonte R, Jain S, Flashman LA, George MS, Grant GA, et al. Randomized placebo-controlled trial of methylphenidate or galantamine for persistent emotional and cognitive symptoms associated with PTSD and/or traumatic brain injury. Neuropsychopharmacology 2016;41:1191-8.
39. Oliver JM, Jones MT, Kirk KM, Gable DA, Repshas JT, Johnson TA, et al. Effect of docosahexaenoic acid on a biomarker of head trauma in American football. Med Sci Sports Exerc 2016;48:974-82.
40. Heileson JL, Anzalone AJ, Carbuhn AF, Askow AT, Stone JD, Turner SM, et al. The effect of omega-3 fatty acids on a biomarker of head trauma in NCAA football athletes: A multi-site, non-randomized study. J Int Soc Sports Nutr 2021;18:65.
41. Mullins VA, Graham S, Cummings D, Wood A, Ovando V, Skulas-Ray AC, et al. Effects of fish oil on biomarkers of axonal injury and inflammation in American football players: A placebo-controlled randomized controlled trial. Nutrients 2022;14:2139.
42. Mullins AV, Snider JM, Michael B, Porter LR, Brinton RD, Chilton FH. Impact of fish oil supplementation on plasma levels of highly unsaturated fatty acid-containing lipid classes and molecular species in American football athletes. Nutr Metab (Lond) 2024;21:43.
43. Breuer LT, Fickling SD, Krause DA, D'Arcy RC, Frizzell TO, Gendron T, et al. The effects of a dietary supplement on brain function and structure in Junior A ice hockey players: A prospective randomized trial. MedRxiv [PrePrint] 2023.
44. Karantali E, Kazis D, McKenna J, Chatzikonstantinou S, Petridis F, Mavroudis I. Neurofilament light chain in patients with a concussion or head impacts: A systematic review and meta-analysis. Eur J Trauma Emerg Surg 2022;48:1555-67.
45. Abdelhak A, Kuhle J, Green AJ. Challenges and opportunities for the promising biomarker blood neurofilament light chain. JAMA Neurol 2023;80:542-3.
46. Shahim P, Politis A, van der Merwe A, Moore B, Chou YY, Pham DL, et al. Neurofilament light as a biomarker in traumatic brain injury. Neurology 2020;95:e610-22.
47. Eggertsen PP, Palmfeldt J, Pedersen AR, Frederiksen OV, Olsen RK, Nielsen JF. Serum neurofilament light chain, inflammatory markers, and kynurenine metabolites in patients with persistent post-concussion symptoms: A cohort study. J Neurol Sci 2024;460:123016.
48. Bramley H, Henson A, Lewis MM, Kong L, Stetter C, Silvis M. Sleep disturbance following concussion is a risk factor for a prolonged recovery. Clin Pediatr (Phila) 2017;56:1280-5.
49. Hoffman NL, O'Connor PJ, Schmidt MD, Lynall RC, Schmidt JD. Relationships between post-concussion sleep and symptom recovery: A preliminary study. J Neurotrauma 2020;37:1029-36.
50. Shekleton JA, Parcell DL, Redman JR, Phipps-Nelson J, Ponsford JL, Rajaratnam SM. Sleep disturbance and melatonin levels following traumatic brain injury. Neurology 2010;74:1732-8.
51. Xie Z, Chen F, Li WA, Geng X, Li C, Meng X, et al. A review of sleep disorders and melatonin. Neurol Res 2017;39:559-65.
52. Händel MN, Andersen HK, Ussing A, Virring A, Jennum P, Debes NM, et al. The short-term and long-term adverse effects of melatonin treatment in children and adolescents: A systematic review and GRADE assessment. EClinicalMedicine 2023;61:102083.
53. Barton C, Falco C. Melatonin administration for sleep disorders in traumatic brain injury: A review of the literature. J Int Soc Phys Rehabil Med 2022;5:46-50.
54. Geller AI, Shehab N, Weidle NJ, Lovegrove MC, Wolpert BJ, Timbo BB, et al. Emergency department visits for adverse events related to dietary supplements. N Engl J Med 2015;373:1531-40.
55. Hensrud DD, Engle DD, Scheitel SM. Underreporting the use of dietary supplements and nonprescription medications among patients undergoing a periodic health examination. Mayo Clin Proc 1999;74:443-7.
56. Kontos AP, Jorgensen-Wagers K, Trbovich AM, Ernst N, Emami K, Gillie B, et al. Association of time since injury to the first clinic visit with recovery following concussion. JAMA Neurol 2020;77:435-40.
57. Mohamadpour M, Whitney K, Bergold PJ. The importance of therapeutic time window in the treatment of traumatic brain injury. Front Neurosci 2019;13:07.
58. Gard A, Vedung F, Piehl F, Khademi M, Wernersson MP, Rorsman I, et al. Cerebrospinal fluid levels of neuroinflammatory biomarkers are increased in athletes with persistent post-concussive symptoms following sports-related concussion. J Neuroinflammation 2023;20:189.
59. Nitta ME, Savitz J, Nelson LD, Teague TK, Hoelzle JB, McCrea MA, et al. Acute elevation of serum inflammatory markers predicts symptom recovery after concussion. Neurology 2019;93:e497-507.
60. Faden AI, Wu J, Stoica BA, Loane DJ. Progressive inflammation-mediated neurodegeneration after traumatic brain or spinal cord injury. Br J Pharmacol 2016;173:681-91.
61. Kenzie ES, Parks EL, Bigler ED, Wright DW, Lim MM, Chesnutt JC, et al. The dynamics of concussion: Mapping pathophysiology, persistence, and recovery with causal-loop diagramming. Front Neurol 2018;9:203.
62. Solnier J, Chang C, Pizzorno J. Consideration for flavonoid-containing dietary supplements to tackle deficiency and optimize health. Int J Mol Sci 2023;24:8663.
63. Halliwell B. Understanding mechanisms of antioxidant action in health and disease. Nat Rev Mol Cell Biol 2024;25:13-33.
64. Dickerman RD, Williamson J, Mathew E, Butt CM, Bird CW,

Hood LE, et al. Branched-chain amino acids are neuroprotective against traumatic brain injury and enhance rate of recovery: Prophylactic role for contact sports and emergent use. Neurotrauma Rep 2022;3:321-32.

65. Kim M, Mok H, Yeo WS, Ahn JH, Choi YK. Role of ginseng in the neurovascular unit of neuroinflammatory diseases focused on the blood-brain barrier. J Ginseng Res 2021;45:599-609.
66. Maier JA, Locatelli L, Fedele G, Cazzaniga A, Mazur A. Magnesium and the Brain: A focus on neuroinflammation and neurodegeneration. Int J Mol Sci 2022;24:223.
67. Husn M, Amin Z, Ali Y, Kanwal L, Sabir K, Shah SA, et al. Neuroprotective effects of Vitamin B1 on memory impairment and suppression of pro-inflammatory cytokines in traumatic brain injury. Metab Brain Dis 2023;38:2175-84.
68. Ikram M, Park HY, Ali T, Kim MO. Melatonin as a potential regulator of oxidative stress, and neuroinflammation: Mechanisms and implications for the management of brain injury-induced neurodegeneration. J Inflamm Res 2021;14:6251-64.
69. Patch CS, Hill-Yardin EL, Lewis M, Ryan L, Daly E, Pearce AJ. The more, the better: High-dose omega-3 fatty acids improve behavioural and molecular outcomes in preclinical models in mild brain injury. Curr Neurol Neurosci Rep 2021;21:45.

Supplementary Table 1: Studies included in review

Author (year)	Study design and setting	Concussion definition	Primary cause of injury	Age (years), mean±SD or median (range)	Intervention drug and dosage	Time since concussion	Duration of treatment	Primary outcome	Primary outcome measure and assessment time	Important findings/ conclusion	Adverse events	Quality
Acute pediatric												
Miller *et al.* (2022) [24]	Single center RCT double-blind placebo outpatient clinic	N/A, diagnosed by sport medicine physician	Sports-related	14–18	DHA DHA 2 g (daily) *n*=20 Placebo group *n*=20	<4 days	12 weeks	mBESS and SCAT3	At enrolment, week 1, 2, 4, and 12	Participants in the DHA group were symptom-free earlier than the placebo group	Eructation (*n*=1)	Fair
Standiford *et al.* (2021) [25]	Single center two-arm randomized cohort study outpatient clinic	N/A; included all patients with GCS >13, chief complaint of headache, head injury, or concussion	Multiple etiologies	12–18	Magnesium + tylenol Magnesium oxide 400mg + Tylenol 500mg (twice daily) *n*=9 Placebo group (Tylenol) Tylenol 500 mg (twice daily) *n*=8	<48 h	5 days	PCSS	Immediately prior to obtaining medications, 1 h, 48 h, and 120 h	Decreases symptoms acutely following a concussion	None reported	Poor
Acute adult												
Kent *et al.* (2023) [26]	Single-center RCT double-blind placebo outpatient clinic	SCAT	Sports-related	20±0.5	Riboflavin 400 mg (daily) *n*=32 Placebo group *n*=28	<24 h	2 weeks	Number of days to recover	Subjectively tailored based on symptom recovery	Lower days to recover in riboflavin group (9.9 days±2.8) compared to placebo (22.2 days±11.5) No adverse effect was reported	None reported	Fair
Corwin *et al.* (2024) [28]	Multi-center RCT double-blind placebo (pilot project) outpatient clinic and ED	4th International conference on concussion in sports	Multiple etiologies	11–34	BCAA valine/ isoleucine/leucine (divided into two doses) BCAA 15 g; *n*=8 BCAA 30 g; *n*=5 BCAA 45 g; *n*=9 BCAA 54 g; *n*=8	<72 h	21 days	Daily computerized neurocognitive test	On day 5, 9, 12, 16, 22, and 24	Reduction of 4.4 points of neurocognitive testing for each 500 gram BCAA consumed No change in cognitive score Lost to follow	Abdominal pain, diarrhea, or bloating especially at high dose group	Fair

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Supplementary Table 1: Contd...

Author (year)	Study design and setting	Concussion definition	Primary cause of injury	Age (years), mean±SD or median (range)	Intervention drug and dosage	Time since concussion	Duration of treatment	Primary outcome	Primary outcome measure and assessment time	Important findings/ conclusion	Adverse events	Quality
					Placebo group *n*=8					up in 42.8% of subject		
Muresanu *et al*. (2015) [23]	Multi-center Retrospective study ED	N/A; included all patients with GCS 13–15	Multiple etiologies	18–95	Cerebrolysin Cerebrolysin 20 mL daily; *n*=615 Cerebrolysin 30 mL daily; *n*=130 Placebo group (standard treatment) *n*=4787	<48 h	Median 10 days	GCS	On day 10 and 30	Higher GOS score in cerebrolysin group on day 10 but no difference on day 30	Diarrhea (<2%)	Poor
Hoffer *et al*. (2013) [27]	Single-center RCT double-blind placebo outpatient clinic	DoD health affairs	Combat related	22 (18–43)	NAC <24 h; *n*=29 Control; *n*=31 26–72 h; *n*=12 Control; *n*=9	<24–72 h	7 days	Concussion symptoms	Before treatment and after treatment	Reduced concussion symptoms in 86% of early group (<24 h) and 42% of the late group (26–72 h) compared to placebo	None reported	Good
Chronic pediatric												
Barlow *et al*. (2020) [29]	Single-center RCT double-blind placebo outpatient clinic	AAN criteria	Multiple etiologies	13.8±2.6	Melatonin (daily) Melatonin 3 mg; *n*=33 Melatonin 10 mg; *n*=33 Placebo group *n*=33	4–6 weeks	28 days	PCSI score	End of 28 days of treatment	There was no significant effect of melatonin compared to placebo in PCSI. Concussions symptoms are improved overtime	Fatigue, cognitive complain, nausea, behavioral change, and insomnia *n*=7 (14%)	Poor
Barlow *et al*. (2021) [30] (secondary analysis of Barlow 2020)	Single-center RCT double-blind placebo outpatient clinic	AAN criteria	Multiple etiologies	14±2.6	Melatonin (daily) Melatonin 3 mg; *n*=25 Melatonin 10 mg; *n*=25 Placebo group *n*=22	4–6 weeks	28 days	Sleep-related problems in PCSI score	Weekly during treatment, 3 months after treatment, and 6 months postinjury	Melatonin was effective in increasing SRP and sleep duration, as well as reducing depressive symptoms after MTBI		Fair

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Author (year)	Study design and setting	Concussion definition	Primary cause of injury	Age (years), mean±SD or median (range)	Intervention drug and dosage	Time since concussion	Duration of treatment	Primary outcome	Primary outcome measure and assessment time	Important findings/ conclusion	Adverse events	Quality
										Melatonin did not improve pain or anxiety		
Iyer *et al*. (2020) [31] (use the same subject as Barlow 2020)	Single-center RCT double-blind placebo outpatient clinic	AAN criteria	Multiple etiologies	14±2.6	Melatonin (daily) Melatonin 3 mg; *n*=22 Melatonin 10 mg; *n*=20 Placebo group *n*=20	4–6 weeks	28 days	Functional connectivity of resting state MRI, and structural gray matter volume	Neuroimaging 1 day before treatment and repeated during the week following treatment	Increase in functional connectivity of posterior DMN regions, corresponded with wake periods reduce wakefulness after sleep onset. Improve sleep symptoms when gray matter volume in posterior cingulate cortex was increased		Good
Howell *et al*. (2021) [32]	Single-center retrospective longitudinal study outpatient clinic	5th International conference on concussion in sports	Sports-related	14.4±2	Melatonin Unclear dose and compliance; *n*=35	<14 days	7–21 days	Health and behavior inventory	On 1st and 2nd visit, no clear and uniform time of assessment	Sleep problems are associated with more severe concussion symptoms Melatonin prescription were no related to symptoms recovery	Not assessed	Poor
					Chronic adult							
Brenner *et al*. (2020) [36]	Single-center RCT double-blind placebo (pilot project) outpatient clinic	Rivermead Postconcussion Symptoms Questionnaire	Combat related	37.4±6.7	Probiotic *Limosilactobacillus reuteri* (daily) *n*=16 Placebo group *n*=15	>6 months	8 weeks±2 weeks daily	The CAPS-5	End of supplementation	No reduction in the CAPS-5 decrease in CRP	None reported	Fair

Contd...

Supplementary Table 1: Contd...

Author (year)	Study design and setting	Concussion definition	Primary cause of injury	Age (years), mean±SD or median (range)	Intervention drug and dosage	Time since concussion	Duration of treatment	Primary outcome	Primary outcome measure and assessment time	Important findings/ conclusion	Adverse events	Quality
Rippee *et al.* (2020) [37]	Single-center nonrandomized study without control (pilot project) outpatient clinic	N/A	Multiple etiologies	45.3±12.2	VHF-KD 5%–10%, carbohydrate 70%–75% fat, and 20%–25% protein; *n*=11	<4 weeks	2 months	Postconcussion assessment and cognitive testing (ImPACT), M-BESS, and PCSS	ImPACT and M-BESS at baseline and month 2 PCSS at baseline, month 1 and 2	Visual memory domain of the ImPACT improved by 12 points (*P*=0.02) and PCSS scores improved by 9 points, although not statistically significant	Diarrhea (*n*=1), nausea (*n*=1), and fatigue (*n*=1)	Poor
Theadom *et al.* (2013) [33]	RCT double-blind placebo (pilot project) outpatient clinic	N/A; The presence of one or more of the following Confusion or disorientation Loss of consciousness; Posttraumatic amnesia Other neurological abnormalities	Multiple etiologies	21–64	Pine bark extract (Enzongenol) Group A (6 weeks of placebo capsule --> 6 weeks of enzogenol (1 g daily) -->4 weeks of placebo capsule); *n*=27 Group B (6 weeks of enzogenol (1 g daily) --> 6 weeks of enzogenol (1 g daily) --> 4 weeks of placebo capsule); *n*=23	3–12 months	6–12 weeks	Rivermead Postconcussion Symptoms Questionnaire, CFQ, WAIS version 4, and HADS	At baseline, week 6, 12, and 16	Improvements in the frequency of self-reported cognitive failures. Other outcome measures showed some positive trends but no significant treatment effects	Headaches (enzogenol=2, placebo=2), sleep disturbance (enzogenol=1, placebo=1), blurred vision (placebo=1)	Fair
Walter *et al.* (2017) [34]	RCT double-blind nondifferentiable placebo	N/A	Sports-related	18–24	Pine bark extract (Enzongenol) Enzogenol 500 mg (twice daily); *n*=21 Placebo group *n*=21	6 months–3 years	6 weeks	HeadRehab's VR system, Stroop Color-Word Test, Beatty Pre- and Posttest Fatigue Rating scale, and EEG	At baseline and week 6	May improve neurocognitive functions and physical symptoms in the chronic phase of concussive injury. Enhanced frontal-midline theta, and decreased parietal theta	Not assessed	Good

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Supplementary Table 1: Contd...

Author (year)	Study design and setting	Concussion definition	Primary cause of injury	Age (years), mean±SD or median (range)	Intervention drug and dosage	Time since concussion	Duration of treatment	Primary outcome	Primary outcome measure and assessment time	Important findings/ conclusion	Adverse events	Quality
										power, indicating reduced mental fatigue. Subjects enrolled in the Enzogenol® group also self-reported reduced mental fatigue and sleep problems		
McAllister *et al*. (2016) [38]	Multi-center RCT double-blind placebo (pilot project) outpatient clinic	Postmorbid Cognitive Scale of the ruff neurobehavioral inventory	Combat related	18–55	Galantamine Galantine 4 mg at week 0 -->8 mg at week 4 --> 12 mg at week 8 --> tapered to 8 mg at week 13 --> 4 mg at week 14; *n*=11 Methylphenidate Methylphenidate 5 mg at week 0 --> 10 mg at week 4 --> 20 mg at week 8 --> tapered to to 10 mg at week 13 --> 5 mg at week 14; *n*=9 Placebo group *n*=12	>3 months	12 weeks of treatment + 2 weeks of taper	Ruff neurobehavioral inventory, Rivermead Postconcussion Symptoms Questionnaire, and posttraumatic stress disorder checklist	At baseline, week 4, 8, and 12	Methylphenidate improves cognitive complaints, Rivermead postconcussive symptoms, and posttraumatic stress symptoms. No significant effect at galantamine group	No serious adverse event. Adverse event was reported in 7/11 participants in Galantamine group, but did not differ from placebo	Fair
Korshnyak *et al*. (2022) [35]	Single-center Longitudinal prospective study outpatient clinic	Convergence insufficiency, small-swinging horizontal nystagmus, pain at the exit points of the occipital nerve, sensitivity disorders, anisoreflexia,	Combat related	28–43	Korean ginseng 80cc red Korean ginseng (2/3 times daily) *n*=42	4–6 years	1 months	Normalization of autonomic reactivity	Before treatment and after treatment	Improves vegetative nervous system, increase melatonin serum level	None reported	Poor

Contd...

Supplementary Table 1: Contd...

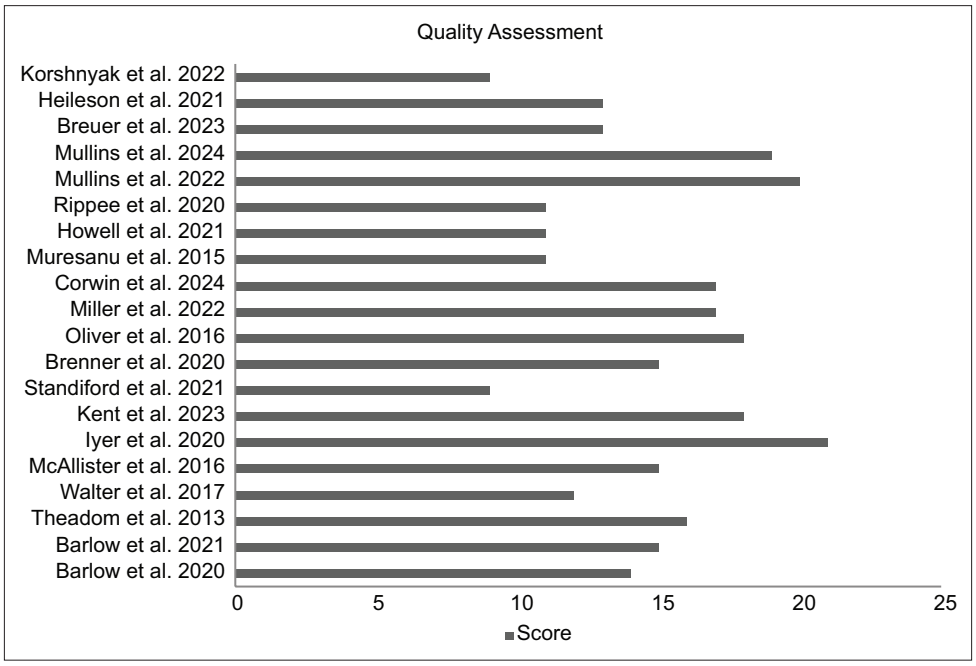
Author (year)	Study design and setting	Concussion definition	Primary cause of injury	Age (years), mean±SD or median (range)	Intervention drug and dosage	Time since concussion	Duration of treatment	Primary outcome	Primary outcome measure and assessment time	Important findings/ conclusion	Adverse events	Quality
		decreased muscle strength in the extremities, impaired coordination and sleep, severe general weakness, drowsiness during the day and VNS deviations - cutis marmorata on the hands, acrocyanosis, distal hyperhidrosis, palpitations, fluctuations in blood pressure										
					Preventive measure							
Oliver *et al*. (2016) [39]	Single-center RCT double-blind placebo	N/A	Sports-related (American Football)	18–23	DHA DHA 2 g; *n*=21 DHA 4 g; *n*=19 DHA 6 g; *n*=22 Placebo group *n*=19	Prevention measure	27 weeks	Serum NFL protein	At the end of supplementation	Reduction of serum NFL concentration in treatment groups, regardless of the dose	Abdominal discomfort (*n*=4), halitosis (*n*=1)	Fair
Mullins *et al*. (2022) [41]	Single-center RCT double-blind placebo	N/A	Sports-related (American Football)	18–23	DHA + EPA DHA + EPA 3.5g (5 days/week); *n*=12 Placebo group (sunflower oil) *n*=17	Prevention measure	26 weeks	Plasma fatty acid and serum NFL concentration	Plasma fatty acid at baseline, week 8, 12, 17, 21, 26, and 33 NFL concentration at baseline, week 17, and 26	Increase plasma DHA and EPA during treatment Return of DHA to baseline value 7 weeks after the end of treatment increase of NFL concentration overtime, no significant difference between groups at any time point	Acne, GI discomfort, and halitosis	Good

Contd...

Supplementary Table 1: Contd...

Author (year)	Study design and setting	Concussion definition	Primary cause of injury	Age (years), mean±SD or median (range)	Intervention drug and dosage	Time since concussion	Duration of treatment	Primary outcome	Primary outcome measure and assessment time	Important findings/ conclusion	Adverse events	Quality
Mullins *et al*. (2024) [42]	Single-center RCT double-blind placebo	N/A	Sports-related (American Football)	18–23	DHA + EPA DHA 2.4 g + EPA 1 g (contain ethyl esters of 407 mg DHA + 170 mg EPA) (5 days/ week); *n*=12 Placebo group (sunflower oil) *n*=17	Prevention measure	26 weeks	Free fatty acid concentration and PC	Week 17, 21, and 26	Increase of PC containing DHA and EPA at all points	Acne, GI discomfort, and halitosis	Fair
Heileson *et al*. (2021) [40]	Multi-center nonrandomized study with parallel control	N/A	Sports-related (American Football)	>18	DHA + EPA + DPA DHA 2 g + EPA 560 mg + DPA 320 mg (>4 times/ week); *n*=31 Control group *n*=35	Prevention measure	89 days	Serum NFL protein	Baseline, end of preseason, and throughout the competitive season	Small unsignificant change of NFL in treatment groups compared to control group	Not assessed	Poor
Breuer *et al*. (2023) [43]	RCT with placebo	Sideline Concussion Assessment Tool (SCAT5)	Sports-related (ice Hockey)	18.73±0.69	Synaquell Synaquell 7.7 g (twice daily); *n*=15 Placebo group *n*=15	Prevention measure	84 days for NA3HL, 112 days for NAHL	NeuroCatch®, King-Devick Test, and NfL chain, SCAT5, PHQ-4, PGIC, and nQoL Short Form 2.0 - cognitive function	Pre- and post-season	Improvements in auditory response and King-Devick Test in treatment group, increase cognitive processing and auditory response increase in placebo group	Not assessed	Poor

DHA: Docosahexaenoic acid, mBESS: Modified balance error scoring system, SCAT3: Sport concussion assessment tool-3, PCSS: Postconcussion severity score, CAT5: Sport concussion assessment tool-5, CAPS-5: Clinician Administered PTSD Scale-5, VHF-KD: Very High-Fat Ketogenic Diet, CFQ: Cognitive Failures Questionnaire, WAIS: Wechsler Adult Intelligence Scale, HADS: Hospital Anxiety and Depression Scale, NFL: Neurofilament light, PHQ-4: Patient Health Questionnaire-4, PGIC: Patient global impression of change, nQoL: Neuro-quality of life, DMN: Default mode network, GOS: Glasgow Outcome Scale, RCT: Randomized controlled trials, N/A: Not available, NAC: N-acetylcsyteine, BCAA: Branched-chain amino acids, AAN: American Academy of Neurology, EEG: Ectroencephalography, PC: Phosphatidylcholine, EPA: Eicosapentaenoic acid, DPA: Docosapentaenoic acid, PCSI: Postconcussion symptom inventory, MRI: Magnetic resonance imaging, CRP: C-reactive protein, MTBI: Mild traumatic brain injury, SD: Standard deviation, ED: Emergency department; VNS: Vegetative nervous system



Supplementary Figure 1: Quality assessment

We used Downs and Black Checklist (DBC) as quality assessment tool for qualitative study. This tool consists of 27 questions as follow:

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the subjects included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of subjects lost to follow-up been described?
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?
16. If any of the results of the study were based on "data dredging", was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention/s reliable?
20. Were the main outcome measures used accurate (valid and reliable)?
21. Were the subjects in different intervention groups or were they recruited from the same population?
22. Were study subjects in different intervention groups or were they recruited over the same period of time?
23. Were study subjects randomised to intervention groups?
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26. Were losses of subjects to follow-up taken into account?
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Barlow *et al*. 2020 [29]	•	•	•	•	?	•	•	o	?	•	o	o	o	o
Barlow *et al*. 2021 [30]	•	•	•	•	?	•	•	o	?	o	o	o	•	•
Theadom *et al*. 2013 [33]	•	•	•	•	?	•	•	o	?	o	•	•	•	•
Walter *et al*. 2017 [34]	•	•	•	•	?	•	o	•	?	•	•	•	•	o
McAllister *et al*. 2016 [38]	•	•	•	•	?	•	•	o	?	•	o	o	•	•
Iyer *et al*. 2020 [31]	•	•	•	•	?	•	o	o	?	•	•	•	•	•
Kent *et al*. 2023 [26]	•	•	•	•	•	•	•	?	o	•	o	o	•	•
Standiford *et al*., 2021 [25]	•	•	?	•	o	•	o	?	o	•	o	o	•	o
Brenner *et al*. 2020 [36]	•	•	•	•	?	•	?	•	o	?	•	•	•	•
Oliver *et al*. 2016 [39]	•	•	•	•	?	•	•	•	o	•	o	o	•	•
Miller *et al*. 2022 [24]	•	•	•	•	?	•	o	•	o	o	•	o	•	•
Corwin *et al*. 2024 [28]	•	•	•	•	?	•	o	•	?	o	O	o	•	•
Muresanu *et al*. 2015 [23]	•	•	•	•	?	•	o	•	o	o	O	O	•	o
Howell *et al*., 2021[32]	•	•	•	•	?	•	?	o	o	•	o	O	o	o
Rippee *et al*. 2020 [37]	•	•	•	•	?	•	?	•	o	•	o	o	•	o
Mullins *et al*. 2022 [41]	•	•	•	•	?	•	•	•	?	•	o	O	•	•
Mullins *et al*. 2024 [42]	•	•	•	•	?	•	•	?	o	•	o	o	•	•
Breuer *et al*. 2023 [43]	•	•	•	•	?	•	?	o	o	•	o	o	?	•
Heileson *et al*. 2021 [40]	•	•	•	•	?	•	•	o	o	•	o	O	•	O
Korshnyak *et al*. 2022 [35]	•	•	•	•	?	•	o	•	o	•	o	o	o	o

Study	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Q25	Q26	Q27
Barlow *et al*. 2020 [29]	o	o	•	•	•	•	•	•	•	o	?	•	o
Barlow *et al*. 2021 [30]	•	o	•	•	•	•	•	•	•	•	•	•	•
Theadom *et al*. 2013 [33]	•	o	•	•	•	•	•	•	•	•	•	•	o
Walter *et al*. 2017 [34]	o	?	•	•	•	•	•	•	o	?	o	o	•
McAllister *et al*. 2016 [38]	•	o	•	•	•	•	•	•	•	•	o	•	o
Iyer *et al*. 2020 [31]	•	?	•	•	•	•	•	•	•	•	o	•	•
Kent *et al*. 2023 [26]	•	o	o	•	•	•	o	•	•	•	?	o	•
Standiford *et al*., 2021 [25]	o	o	o	•	?	•	o	o	•	o	o	o	o
Brenner *et al*. 2020 [36]	•	o	o	•	•	•	•	•	•	•	?	o	o
Oliver *et al*. 2016 [39]	•	o	o	•	•	•	o	•	•	•	?	o	•
Miller *et al*. 2022 [24]	•	o	o	•	•	•	•	•	•	•	o	o	o
Corwin *et al*. 2024 [28]	•	o	•	•	?	•	•	•	•	•	?	•	o
Muresanu *et al*. 2015 [23]	?	o	?	•	o	•	o	•	o	•	o	o	o
Howell *et al*., 2021 [32]	o	o	?	•	o	•	o	?	o	?	?	o	o
Rippee *et al*. 2020 [37]	o	o	o	•	•	•	?	o	o	o	o	?	o
Mullins *et al*. 2022 [41]	•	o	•	•	•	•	•	•	•	•	?	o	•
Mullins *et al*. 2024 [42]	•	o	•	•	•	•	•	•	•	•	?	o	•
Breuer *et al*. 2023 [43]	•	o	o	•	•	•	o	•	•	o	?	o	o
Heileson *et al*. 2021 [40]	o	o	?	•	•	•	o	•	o	o	?	o	•
Korshnyak *et al*. 2022 [35]	o	o	o	•	o	•	o	o	o	o	o	o	o