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REVIEW

Nutritional interventions to improve neurophysiological impairments following traumatic brain injury: A systematic review

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Abstract

Traumatic brain injury (TBI) accounts for significant global health burden. Effects of TBI can become chronic even following mild injury. There is a need to develop effective therapies to attenuate the damaging effects of TBI and improve recovery outcomes. This literature review using a priori criteria (PROSPERO; CRD42018100623) summarized 43 studies between January 1998 and July 2019 that investigated nutritional interventions (NUT) delivered with the objective of altering neurophysiological (NP) outcomes following TBI. Risk of bias was assessed for included studies, and NP outcomes recorded. The systematic search resulted in 43 of 3,748 identified studies met inclusion criteria. No studies evaluated the effect of a NUT on NP outcomes of TBI in humans. Biomarkers of morphological changes and apoptosis, oxidative stress, and plasticity, neurogenesis, and neurotransmission were the most evaluated NP outcomes across the 43 studies that used 2,897 animals. The risk of bias was unclear in all reviewed studies due to poorly detailed methodology sections. Taking these limitations into account, anti-oxidants, branched chain amino acids, and ω-3 polyunsaturated fatty acids have shown the most promising pre-clinical results for altering NP outcomes following TBI. Refinement of pre-clinical methodologies used to evaluate effects of interventions on secondary damage of TBI would improve the likelihood of translation to clinical populations.

KEYWORDS

animal models, biomarker, clinical, nutrition, rehabilitation, supplementation

1 | INTRODUCTION

Traumatic brain injury (TBI) has been referred to as a silent epidemic, with an estimated age standardized global incidence rate of 369 per 100,000 person-years and an estimated incidence of 27 million new TBIs per year (James et al., 2019; Rusnak, 2013). The true incidence of TBI may be even higher due to reporting and recording limitations (Barker-Collo et al., 2016). Injury burden is undeniable; yet due to intricate TBI pathophysiology, clinical strategies to attenuate damage and assist recovery across the TBI spectrum remain elusive. Mild, moderate, and severe TBIs are characterized by a primary biomechanical event wherein force is transmitted, injuring the brain as a consequence of events such as a fall, motor vehicle accident (MVA), assault, blast exposure, or sport-related activity (Gardner & Zafonte, 2016). TBI severity is primarily determined using the Glasgow Coma Score (assessment of level of consciousness). Additionally, moderate and severe TBIs are

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typically associated with skull fracture and/or positive neuroimaging findings indicating structural damage (Saatman et al., 2008; K. Wang et al., 2016). Mild TBI (mTBI) represents the majority (95%) of TBIs and is generally classified based on a Glasgow Coma Score between 13 and 15, symptom complaints, and the absence of both skull fracture and positive neuroimaging (Feigin et al., 2013; Saatman et al., 2008; Wang, Cui, et al., 2016). Within minutes of the traumatic event (primary injury) neurological homeostasis is disrupted representing the secondary injury phase of TBI. Neurophysiological (NP) consequences of TBI can include: ionic and neurometabolic dysregulation; neurovascular and autonomic uncoupling; axonal and cytoskeletal damage; impaired synaptic plasticity; neuroinflammation; disrupted blood–brain barrier (BBB) permeability and damaged cell membranes; impaired synaptic plasticity; and neuronal apoptosis (see Romeu-Mejia et al., 2019 for a recent review detailing TBI pathophysiology).

Improved understanding of NP consequences of TBI provides targets for therapeutic interventions to improve recovery outcomes (Romeu-Mejia et al., 2019; Wang, Cui, et al., 2016). On this basis, targeted exercise prescription has been shown to be an effective intervention to address symptom burden and functional deficits that commonly occur as a consequence of TBI (Alsalaheen et al., 2010; Archer et al., 2012; Baker et al., 2012; Ellis, Cordingley, et al., 2015; Ellis et al., 2016; Ellis, Leddy, et al., 2015; Fernandes et al., 2017; Gomez-Pinilla et al., 2008; Griesbach et al., 2004, 2009; Leddy et al., 2007, 2013, 2016; Storey et al., 2018). Some symptoms such as headache complaints, sleep disruption, and/or mood disorders, that can occur secondary to TBI, have been managed with prescription pharmaceuticals (although greater clarity regarding efficacy of these approaches is needed) (Bhatnagar et al., 2016; Liu et al., 2019; Meehan, 2011; Miller Phillips & Reddy, 2016; Plantier & Luauté, 2016). However, there is no intervention to proactively target the secondary injury phase of TBI in a manner that promotes earlier resolution of a range of symptom complaints and deficits observed clinically (Mohamadpour et al., 2019).

Lifestyle factors such as diet and nutrition play crucial roles in maintaining neurological function and overall brain health (Gomez-Pinilla, 2011). In this regard, modification of dietary intake and/or nutritional supplementation post-TBI demonstrate potential to attenuate damaging effects of secondary injury following TBI by simultaneously acting upon multiple NP pathways. An advantage of nutritional interventions (NUT) is the "over-the-counter" accessibility of affordable food and supplements which could potentially benefit patients post-TBI to alter the secondary damage of TBI when availability of medical services may be limited. Modifying nutrition is potentially useful for enhancing resilience to the damaging effects of TBI for at risk populations (i.e., military personnel and athletes participating in high-risk sports) (Chakraborty et al., 2016; Oliver et al., 2018). Due to scalability and implementation limitations, the preventative role of nutrition is beyond the scope of the current review.

Cellular damage and dysfunction that characterizes the secondary injury phase of TBI manifest clinically as an array of functional and neurobehavioral deficits (Giza & Hovda, 2014; Kenzie et al., 2018). Previous reviews in the field of TBI have not summarized relevant NUT literature both comprehensively and systematically, or have focussed on interventions that target observable clinical symptoms (Ashbaugh & McGrew, 2016; Bothe & Stover, 2015; Davies, 2018; Lewis, 2016; Lukaski & Hardy, 2013; McDougall et al., 2018; Sharma et al., 2018; Trojian et al., 2017; White & Venkatesh, 2011). This review evaluated the evidence for treatments to reduce the physiological causes of these clinical symptoms through exploring the effect of NUTs on NP outcomes.

Significance

Cellular damage and impaired neurophysiological function are the hallmarks of traumatic brain injury (TBI) pathophysiology. Over the last 20 years, nutritional interventions have demonstrated potential to blunt these damaging effects in a manner that may improve recovery outcomes, however, this literature has never been systematically consolidated. This review sought to identify nutritional interventions with "over-the-counter" potential to benefit clinical patients with TBI. This study is significant in identifying that the relationship between nutritional interventions and TBI pathophysiology has only been evaluated in animal studies; and many studies have considerable methodological limitations that threaten the likelihood of translation to clinical populations.

1.1 | Aim

This review aimed to systematically consolidate evidence from animal and human studies, evaluating NUTs administered post-TBI and their subsequent effects on NP outcomes.

2 | METHODS

We conducted this review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and followed clear a priori criteria registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018100623). Review methodology was developed according to Population, Intervention, Comparator, and Outcome (P.I.C.O.) guidelines (Table 1).

2.1 | Search strategy and study selection criteria

Table 1 outlines search terms to identify studies investigating the influence of nutritional and dietary manipulation interventions on NP

TABLE 1 Search strategy and study eligibility criteria

Systematic search strategy		
TBI-related search terms	Postconcussion or "post-concussion" or concussion or tbi or mtbi or "traumatic brain injur*" or "cortical impact" or "fluid percussion" or "acceleration injury"	
The nutrition- and diet-related search terms below were queried within 10 words before or after TBI-related search terms		
Nutrition- and diet-related search terms	Diet* or supplement* or "neuroprotective agent*" or creatine or antioxidant* or "anti-oxidant*" or "fatty acid*" or vitamin* or nutri* or nutraceutical or keto* or "amino acid*" or "complementary and integrative medicine" or "complementary and alternative medicine"	
P.I.C.O. framework and study selection criteria		
	Exclusion criteria	**Inclusion criteria**
Participants/population	*In vitro* models of brain/neuronal/axonal injury	Mild, moderate, and severe TBI
Humans and/or mammals that have sustained TBI	Spinal cord injury	Single or repetitive impacts/injuries
	Human subjects with TBI on life support, in a comatose state, and/or subjects that are paralysed	*In vivo* investigations including: 1. Clinical studies with human subjects and/or 2. Pre-clinical studies on animal models of TBI
Intervention Nutrition and/or dietary manipulation interventions administered *post-injury* with the aim to attenuate impaired neurophysiological functions due to TBI	Nutrition/dietary interventions administered pre-TBI	Nutrition and/or dietary manipulation interventions administered non-invasively* post-TBI
	Acute lifesaving interventions	
	Administration of nutrition supplement via invasive means such as intravenous, intraperitoneal, intrathecal, or intracerebroventricular/intracerebral injections	
	Nutrition/dietary interventions targeting the gut/intestines after severe TBI	*Exception made for nutrients/supplements delivered via gavage to animal models to ensure dosage compliance
	Enteral feeding for paralysed/comatose subjects	
	Pharmaceutical/drug/hormone interventions	
Comparators/controls Pre-injury baseline measures, current best practice, regular diet, no treatment, sham injury, control, or placebo group	Absence of comparison group	Presence of comparison group
Outcomes Measures of neurophysiological function related to secondary injury phase of TBI	Neurocognitive, neuropsychological, behavioral, or clinical outcome measures only	Minimum of one objective outcome measure to quantify neurophysiological outcomes and/or consequences of TBI including: morphological changes, cell death/apoptosis/cell survival, energy metabolism, mitochondrial function, oxidative stress, glial activation, immune response, BBB integrity, cell membrane homeostasis, plasticity, neurotransmission, and/or neurogenesis

outcomes post-TBI. We filtered titles and abstracts for nutritional and diet-related terms within 10 words either side of TBI-related keywords. When permitted by database functionality, additional filters were applied to limit search results to peer-reviewed studies, available in full-text, and published in English. Our systematic database search identified 4,148 articles (Figure 1) available online and published between January 1998 and July 2019 through MEDLINE [EBSCO] (n = 652), Web of Science (n = 608), Scopus (n = 639), CINAHL [EBSCO] (n = 451), SportDiscus [EBSCO] (n = 245), PsycINFO [OVID] (n = 1,489), and Cochrane Library [Wiley] (n = 62). Reference lists of included articles were reviewed but did not identify any additional results. Once duplicate references were removed, screening for eligibility by JM of titles, abstracts, and full-texts of 3,748 studies was completed. A 10% random check of references was performed at each screening stage by PH. Table 1 provides detailed inclusion and exclusion criteria used to guide study selection.

2.2 | Quality assessment

Only pre-clinical animal studies met all inclusion criteria for this review, so quality and risk of bias (RoB) was assessed for included studies using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) RoB tool (Hooijmans et al., 2014). The SYRCLE RoB tool adapted the Cochrane Collaboration RoB tool (Higgins et al., 2011) for randomized controlled trials (RCTs) using

human subjects adjusting for aspects of bias within animal studies. The 10 signaling questions used within SYRCLE's RoB tool, and respective results for included studies are presented in Table 2. Quality assessment of all included studies was performed by JM with a 10% random check by PH.

2.3 | Data extraction and synthesis

Studies meeting inclusion criteria were recorded and curated for: study characteristics (study type, number of study groups, method of TBI induction, TBI severity, and mortality rate); animal characteristics (species, sample size, sex, age, and weight); intervention details (type of intervention, controls used, timing of initiation of intervention, intervention dosage, and duration of intervention); and outcomes (NP outcomes evaluated, biomarkers used, and behavioral/neurocognitive outcomes). Efforts were made to contact study authors to acquire any key information that was missing or unclear in published articles. A summary of study characteristics (Table 3), summary of NP outcomes (Table 4), and details of NP and behavioral outcomes (Table S1) are provided.

We qualitatively appraised studies, aggregating evidence to identify strengths, weaknesses, and trends suggesting preliminary positive intervention effects from animal studies within this review while identifying gaps in knowledge. Through identifying these trends we can begin to develop explanatory theories about how NUTs may facilitate improved recovery outcomes post-TBI; while generating hypotheses to justify and inform the feasibility of translating this evidence to clinical patients (de Vries et al., 2014; Snilstveit et al., 2012).

3 | RESULTS

3.1 | Article selection and quality assessment

Application of inclusion and exclusion criteria to titles and abstracts of search resulted in 201 full-text articles that were screened for eligibility; 43 journal articles (Bailes & Mills, 2010; Cheng et al., 2016;

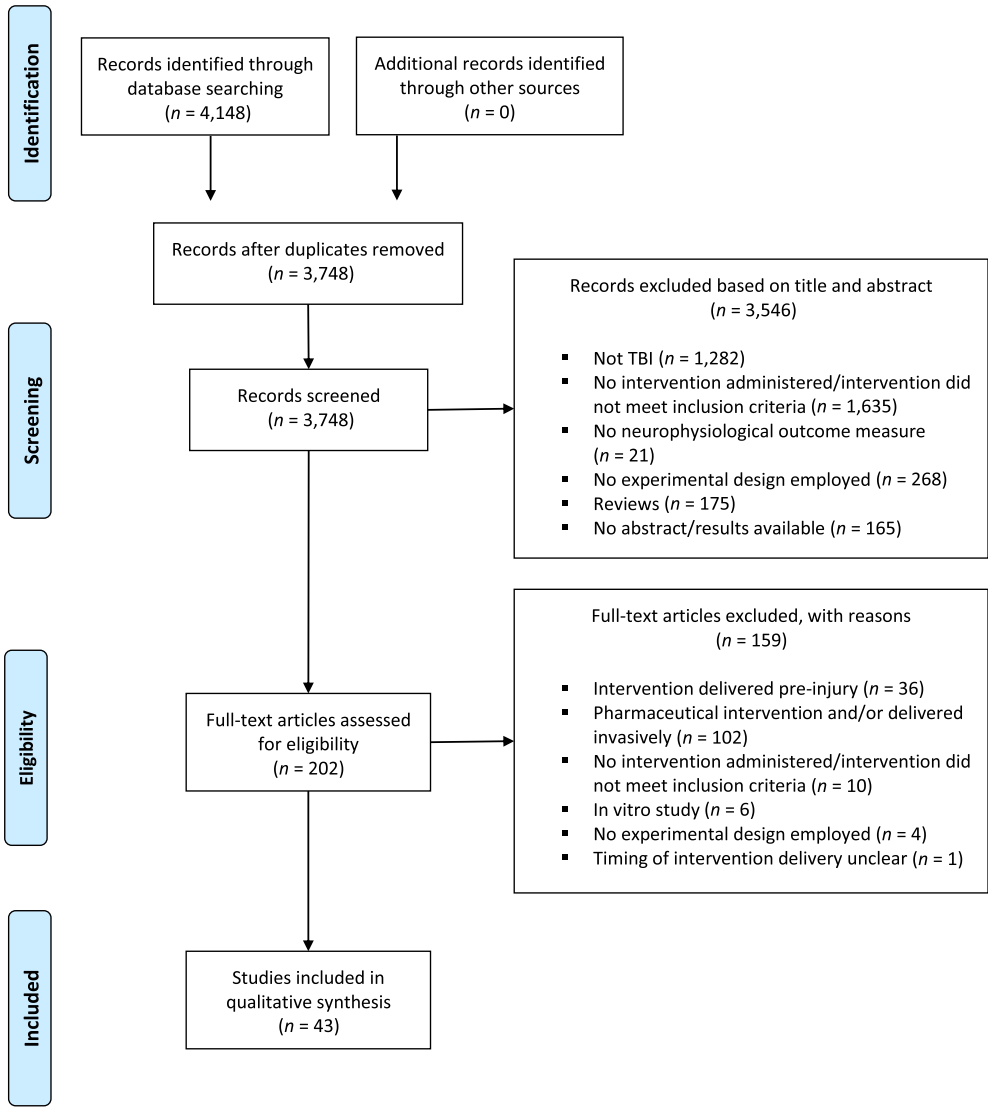

FIGURE 1 PRISMA flowchart [Color figure can be viewed at wileyonlinelibrary.com]

Cole et al., 2010; Davis et al., 2008; Deng-Bryant et al., 2011; Elliott et al., 2018; Gerbatin et al., 2019; Greco et al., 2016; Hu, Wang, Jin, et al., 2009; Hu, Wang, Qiao, et al., 2009; Itoh et al., 2013; Ji et al., 2017; Jiang et al., 2017; Krishna et al., 2019; Kumar et al., 2014; Lim et al., 2013; Liu et al., 2017; Mills et al., 2011; Ozbal et al., 2015; Özevren et al., 2018; Prins et al., 2005; Prins & Hovda, 2009; Rubovitch et al., 2019; Saraiva et al., 2012; Schober et al., 2016; Schwartzkroin et al., 2010; Sharma et al., 2010; Shin & Dixon, 2011; Su et al., 2016; Thau-Zuchman et al., 2019; Toklu et al., 2009; Wang et al., 2018; Wang, Li, et al., 2016; Wang, Zhang, et al., 2016; Wei et al., 2015; Wu et al., 2011, 2014; Xie et al., 2018; Xing et al., 2016; Xu et al., 2017; Zhang et al., 2018; Zhao et al., 2014; Zhu et al., 2017) met all eligibility criteria. Most studies (28/43) were conducted since 2013, with four to seven new studies being released each year since 2016. All studies were pre-clinical animal studies with 27/43 studies clearly stating that randomization took place. RoB was generally unclear across all studies (Table 2) due to limited methodological detail, which failed to address several criteria within the SYRCLE RoB tool such as: "5) Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?" (unclear in 40 of 43 studies); and "6) Were the animals selected at random for outcome assessment?" (unclear in 30 of 43 studies).

3.2 | TBI induction and animal characteristics

3.2.1 | TBI induction

Across the 43 included studies (Table 3), TBIs were produced in 2,897 animals (more animals were used but the sample size in several studies was unclear) using controlled cortical impact (16 CCI studies), fluid percussion injury (12 FPI studies), or weight drop techniques (15 studies). Generally, Feeney's weight drop model (5/15) and CCI are implemented to mimic a mainly focal brain injury that might occur after a fall, MVA, or sport-related TBI (Ma et al., 2019). Marmarou's weight drop model (6/15) produced mainly diffuse brain injury like that following a fall or MVA. To achieve mixed brain injury (with focal and diffuse consequences) FPI is commonly delivered (Ma et al., 2019). No studies used a blast wave model which would mimic TBI commonly suffered by deployed military personnel (Ma et al., 2019; Xiong et al., 2013). Animals were anesthetized in 42 studies prior to delivery of TBI. Craniotomy or skull surgical alteration occurred in 34/43 studies. The head of animals was secured during TBI induction in 15/43 studies, while freedom of head movement was unclear or not reported in 27/43 studies (9 CCI, 10 FPI, 8 weight drop).

3.2.2 | TBI severity

TBI induction methods (Table 3) inflicted mTBI in nine studies (five FPI, four weight drop), moderate TBI in nine studies (one CCI, six FPI, two weight drop), and severe TBI in four studies (one CCI, three weight drop). In 23 studies TBI severity was not clearly described (15 CCI, 2 FPI, 6 weight drop). Given TBI severity was a key variable of interest, study authors were contacted for information, or recently released classification criteria were used to infer TBI severity in Table 3 (Ma et al., 2019; Siebold et al., 2018). One study intentionally compared outcomes after moderate and severe TBI (Davis et al., 2008), otherwise investigations focused on evaluating a NUT following a specific severity of TBI. Two studies evaluated a NUT following repetitive TBI (Wang et al., 2018; Zhang et al., 2018). In both studies animals suffered three TBIs by either FPI or Marmarou weight drop to produce repetitive mild and severe TBIs, respectively.

3.2.3 | Animal characteristics

Most studies investigated NUTs in rat models of TBI (29 used Sprague Dawley rats; six used Wistar rats), the remaining studies used mice (six used C57BL/six mice, two used ICR mice; Table 3) as an animal model of TBI. No interventions were evaluated for utility across multiple species using comparable methodologies. Fasting was studied in both mice and rats following TBI, however, TBI induction and severity modeling was considerably different between studies preventing results comparison. TBI was modeled in only male rats/mice except for one study (Zhu et al., 2017) that included male and female Sprague Dawley rats to evaluate docosahexaenoic acid (DHA) supplementation after FPI.

3.2.4 | Animal maturity

Age and maturity of rodents varied across included studies (Table 3). Animal age was commonly indicated based on the number of days post-natal (PND) at which animals were subject to TBI or sham injury. Insights into the interaction of age and TBI are gained by conducting experiments with animals at differing stages of maturity. Adulthood in rats and mice is considered to begin after PND-56 and PND-42, respectively (Jackson et al., 2017). Included studies used PND-7 to 17 and PND-35 to 55 to define immature/juvenile and adolescent rats, respectively. Juvenile and immature rats were used in three studies, pre-adolescent/adolescent rats in eight studies, and adult rats in 18 studies. All mice studies used late adolescent and adult mice. Animal weight was the only measure of maturity reported in 12 studies. Due to a variety of unreported environmental factors that could affect weight, animal age could not be inferred in these studies. Four studies compared how a KD attenuated NP impairments post-TBI between multiple age groups (primarily pre-adolescent rats vs. adult rats), and identified a trend for the benefits of KD post-TBI being age specific and limited to pre-adolescent rats (Deng-Bryant et al., 2011; Greco et al., 2016; Prins et al., 2005; Prins & Hovda, 2009).

TABLE 2 Included studies RoB evaluated using the SYRCLE tool

	1) Was the allocation sequence adequately generated and applied?	2) Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3) Was the allocation to the different groups adequately concealed during?	4) Were the animals randomly housed during the experiment?	5) Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6) Were the animals selected at random for outcome assessment?	7) Was the outcome assessor blinded?	8) Were incomplete outcome data adequately addressed?	9) Are reports of the study free of selective outcome reporting?	10) Was the study apparently free of other problems that could result in a high risk of bias?
Prins et al. (2005)	UC	Yes	UC	UC	UC	UC	UC	UC	UC	UC
Davis et al. (2008)	UC	Yes	UC	UC	UC	No	UC	No	No	UC
Hu, Wang, Jin, et al. (2009)	Yes	Yes	UC	UC	UC	UC	Yes	UC	Yes	UC
Hu, Wang, Qiao, et al. (2009)	Yes	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Prins and Hovda (2009)	Yes	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Toklu et al. (2009)	Yes	Yes	UC	UC	UC	UC	Yes	UC	Yes	UC
Bailes and Mills (2010)	UC	Yes	UC	No	UC	No	UC	UC	Yes	UC
Cole et al. (2010)	Yes	Yes	UC	UC	UC	UC	Yes	No	Yes	UC
Schwartzkroin et al. (2010)	Yes	Yes	UC	UC	UC	UC	Yes	No	Yes	UC
Sharma et al. (2010)	Yes	Yes	UC	UC	UC	No	UC	UC	Yes	UC
Deng-Bryant et al. (2011)	UC	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Mills et al. (2011)	UC	Yes	UC	UC	UC	No	UC	UC	Yes	UC
Shin and Dixon (2011)	Yes[a]	Yes	UC	UC	UC	UC	No[a]	UC	Yes	UC
Wu et al. (2011)	UC	Yes	UC	UC	UC	No	UC	UC	Yes	UC
Saraiva et al. (2012)	Yes[a]	Yes	UC	UC	UC	UC	Yes[a]	UC	Yes	UC
Itoh et al. (2013)	Yes	Yes	UC	UC	UC	Yes	UC	UC	Yes	UC
Lim et al. (2013)	Yes	Yes	UC	UC	Yes	UC	Yes	UC	Yes	UC
Kumar et al. (2014)	Yes	Yes	UC	No	UC	UC	UC	Yes	Yes	UC
Wu et al. (2014)	UC	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Zhao et al. (2014)	Yes	Yes	UC	UC	UC	Yes	Yes	Yes	Yes	UC
Ozbal et al. (2015)	Yes	Yes	UC	UC	UC	UC	Yes	Yes	Yes	UC
Wei et al. (2015)	Yes	Yes	UC	UC	UC	UC	Yes	Yes	Yes	UC
Cheng et al. (2016)	Yes	Yes	UC	UC	Yes	Yes	Yes	Yes	Yes	UC

(Continues)

TABLE 2 (Continued)

	1) Was the allocation sequence adequately generated and applied?	2) Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3) Was the allocation to the different groups adequately concealed during?	4) Were the animals randomly housed during the experiment?	5) Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6) Were the animals selected at random for outcome assessment?	7) Was the outcome assessor blinded?	8) Were incomplete outcome data adequately addressed?	9) Are reports of the study free of selective outcome reporting?	10) Was the study apparently free of other problems that could result in a high risk of bias?
Greco et al. (2016)	Yes	Yes	UC	UC	UC	UC	No[a]	Yes	Yes	UC
Schober et al. (2016)	UC	Yes	UC	No	UC	Yes	Yes	Yes	Yes	UC
Su et al. (2016)	UC	Yes	UC	UC	UC	No	UC	Yes	Yes	UC
Wang, Cui, et al. (2016)	Yes	Yes	UC	UC	UC	UC	UC	Yes	Yes	UC
Wang, Li, et al. (2016)	Yes	Yes	UC	UC	Yes	UC	Yes	Yes	Yes	UC
Xing et al. (2016)	Yes	Yes	UC	UC	UC	Yes	UC	UC	Yes	UC
Ji et al. (2017)	UC	Yes	UC	No	UC	UC	Yes	No	Yes	UC
Jiang et al. (2017)	UC	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Liu et al. (2017)	Yes	Yes	Yes	UC	UC	UC	Yes	No	Yes	UC
Xu et al. (2017)	Yes	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Zhu et al. (2017)	Yes	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Elliott et al. (2018)	Yes	Yes	UC	UC	UC	UC	Yes	No	Yes	UC
Özevren et al. (2018)	UC	Yes	UC	UC	UC	UC	UC	Yes	Yes	UC
Wang et al. (2018)	Yes	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Xie et al. (2018)	Yes	Yes	UC	UC	UC	No	UC	UC	Yes	UC
Zhang et al. (2018)	Yes	Yes	UC	No	UC	UC	Yes	UC	Yes	UC
Gerbatin et al. (2019)	Yes	Yes	UC	UC	UC	UC	Yes	UC	Yes	UC
Krishna et al. (2019)	UC	Yes	UC	UC	UC	UC	UC	No	Yes	UC
Rubovitch et al. (2019)	UC	Yes	UC	UC	UC	UC	UC	UC	Yes	UC
Thau-Zuchman et al. (2019)	Yes	Yes	UC	UC	UC	Yes	Yes	Yes	Yes	UC
Yes	29	43	1	0	3	6	18	12	43	0
No	0	0	0	5	0	7	2	7	0	0
Unclear	14	0	42	38	40	30	23	24	0	43

[a]Information acquired by contacting corresponding author.

Abbreviation: UC, unclear in published article.

TABLE 3 Study design and intervention details

Author (year) *country*	Animal study type (# of study groups)	Method of TBI delivery, TBI severity, mortality rate	Animal details (*N*)	Intervention	Controls	Initiation of intervention (duration of intervention)	Dosage
Anti-oxidants							
Toklu et al. (2009) *Turkey*	Random pre-clinical (*n* = 4)	MIAI, Mild, UC	300–350 g; Wistar rats (64)	α-Lipoic acid via gavage	Sham + vehicle; sham + α-lipoic acid; TBI + vehicle	First dose 30 min post-injury then 1 dose 24 hr later (48 hr)	100 $mg^{-1}kg^{-1}day$
Ji et al. (2017) *China*	Pre-clinical (*n* = 3)	M.A. Flierl weight drop model, Mod, 8%	28–32 g; ICR mice (UC)	Astaxanthin diluted in olive oil (1 ml/kg) via gavage	Sham + olive oil; TBI + olive oil	First dose 30 min post-injury then 1 dose per 24 hr until sacrifice (7 days)	75 $mg^{-1}kg^{-1}day$
Jiang et al. (2017) *China*	Pre-clinical (*n* = 7)	CCI, Mod[a], NR	Adult; 200–240 g; *SD* rats (UC)	Catechin supp via gavage at 5 dosages	Sham; TBI + vehicle	One dose per day until sacrifice (24 hr or 28 days)	Dose 1:1 mg/kg; dose 2:5 mg/kg; dose 3:10 mg/kg; dose 4:20 mg/kg; dose 4:30 mg/kg
Krishna et al. (2019) *USA*	Pre-clinical (*n* = 3)	FPI, Mod, NR	PND-70; *SD* rats (UC)	5% Blueberry-enriched diet	Sham + Std diet; TBI + Std diet	Immediately post-injury (14 days)	Fed *ad libitum*
Itoh et al. (2013) *Japan*	Random pre-clinical (*n* = 3)[b]	CCI, Mod to severe[a], NR	PND-42; 120–140 g; Wistar rats (123)	EGCG dissolved in drinking water	Sham + regular drinking water; TBI + regular drinking water	Immediately post-injury (24 hr, 72 hr, 7 days)	0.1% EGCG drinking water; drank *ad libitum*
Cheng et al. (2016) *China*	Random pre-clinical (*n* = 6)	CCI, Mod to severe[a], 7%	PND-56 to PND-84; 20–26 g; 151 wild type, 31 Nrf2 knockout; C57BL/6 mice (182)	(-)-Epicatechin supp via gavage in low, moderate, high dose	Sham + vehicle; TBI + vehicle	First dose 3 hr post-injury then 1 additional per 24 hr for 3 or 7 days (72 hr dosage differences or 7 days moderate dose only)	Low (-)-epicatechin: 5 $mg^{-1}kg^{-1}day$; moderate (-)-epicatechin: 15 $mg^{-1}kg^{-1}day$; high (-)-epicatechin: 45 $mg^{-1}kg^{-1}day$
Ozbal et al. (2015) *Turkey*	Random pre-clinical (*n* = 3)	Weight drop, NR, NR	Juvenile; PND-7; 20–30 g; Wistar rats (42)	α-Lipoic acid via gavage	Sham + Std diet; TBI + Std diet	First dose 30 min post-injury then 1 additional dose 24 hr later (48 hr)	100 $mg^{-1}kg^{-1}day$
Wei et al. (2015) *China*	Random pre-clinical (*n* = 5)	Feeney weight drop, NR, NR	250–280 g; *SD* rats (150)	α-Lipoic acid in low and high dose via gavage	Sham + vehicle; sham + α-lipoic acid; TBI + vehicle;	First dose 30 min post-injury then 1 dose 24 hr later (48 hr)	Low α-lipoic acid: 20 mg/kg; high α-lipoic acid 100 mg/kg
Branched chain amino acids							
Lim et al. (2013) *USA*	Random pre-clinical (*n* = 3)	FPI, Mild, 0%[c]	PND-35 to PND-49; 20–25 g; C57BL/J6 mice (19)	Tap water containing valine, leucine, and isoleucine	Sham + tap water; TBI + tap water	Immediately post-injury (4 weeks)	100 mM of each BCAA dissolved in tap water; Drank *ad libitum*

(Continues)

TABLE 3 (Continued)

Author (year) *country*	Animal study type (# of study groups)	Method of TBI delivery, TBI severity, mortality rate	Animal details (*N*)	Intervention	Controls	Initiation of intervention (duration of intervention)	Dosage
Elliott et al. (2018) *USA*	Random pre-clinical ($n = 3$)	FPI, Mild, 0%[c]	PND-35 to PND-49; 20–25 g; C57BL/J6 mice (24)	Tap water containing valine, leucine, and isoleucine	Sham + tap water; TBI + tap water	Initiated 48 hr post-injury (5 days)	100 mM of each BCAA dissolved in tap water; Drank *ad libitum* (approx 3–5 ml/day)
Cole et al. (2010) *USA*	Random pre-clinical ($n = 4$)	Lateral FPI, Mild to Mod, 0%	PND-35 to PND-49; 20–25 g; C57BL/6 mice (UC)	Tap water containing valine, leucine, and isoleucine; or tap water containing phenylalanine	Sham + tap water; TBI + tap water	Initiated 48 hr post-injury (5 days)	100 mM of each BCAA dissolved in tap water; Drank *ad libitum*
Creatine							
Saraiva et al. (2012) *Brazil*	Pre-clinical ($n = 2$)	FPI, Mod[c], 18.07%[c]	Adult; 250–300 g; Wistar rats (~24 to 40)	Creatine supp via gavage	Sham + vehicle; sham + creatine supp; TBI + vehicle	First dose 30 min post-injury then 1 dose per 24 hr until sacrifice (72 hr)	300 $mg^{-1}kg^{-1}day$
Gerbatin et al. (2019) *Brazil*	Random pre-clinical ($n = 4$)	FPI, Mod, 18.07%	PND-90; Wistar rats (166)	Creatine supp via gavage	Sham + Std diet; sham + creatine supp; TBI + Std diet	Initiated 7 days post-injury then 1 dose per 24 hr until sacrifice (4 weeks)	300 $mg^{-1}kg^{-1}day$
Fasting and caloric restriction							
Liu et al. (2017) *China*	Random pre-clinical ($n = 3$)	Weight drop, Mild, NR	PND-84; C57BL/6 mice (45)	Caloric restriction	TBI + normal caloric intake; TBI + high energy intake	Feeding initiated 6–10 hr post-injury (24 hr, 48 hr, 35 days, or 37 days)	High energy: normal caloric intake × 1.3; caloric restriction: 0.7 × normal caloric intake; fed *ad libitum* according to energy ratio;
Rubovitch et al. (2019) *Israel*	Pre-clinical ($n = 7$)	Weight drop, Mild, NR	PND-42 to PND-49; ICR mice (177)	Intermittent fasting or caloric restriction	Sham + Std caloric intake; sham + fasting; sham + caloric restriction; TBI + Std caloric intake	Immediately post-injury (30 days)	Intermittent fasting: alternating 24 hr periods with/without access to food; Caloric restriction fed *ad libitum* according to energy ratio: 10% restriction week 1, 20% restriction week 2, 30% restriction week 3, 40% restriction until sacrifice

(Continues)

TABLE 3 (Continued)

Author (year) *country*	Animal study type (# of study groups)	Method of TBI delivery, TBI severity, mortality rate	Animal details (*N*)	Intervention	Controls	Initiation of intervention (duration of intervention)	Dosage
Davis et al. (2008) *USA*	Pre-clinical ($n = 5$)[b]	CCI, Mod and severe, NR	Adult; *SD* rats (30)	Fasting	TBI + regular *ad libitum* feeding	Immediately post-injury (24 hr or 48 hr)	No caloric intake for designated time period
Ketogenic diet (KD)							
Zhang et al. (2018) *China*	Random pre-clinical ($n = 3$)	FPI × 3, Mild, NR	PND-60; 100–140 g; *SD* rats (72)	KD	TBI + Std diet; Sham + Std diet	Immediately post-injury (7 days)	Fed *ad libitum*
Prins et al. (2005) *USA*	Pre-clinical ($n = 20$)	CCI, Mod[a], NR	PND-17 ($n = 27$), PND-35 ($n = 29$), PND-45 ($n = 27$), PND-65 ($n = 26$); *SD* rats (109)	KD	TBI + Std diet; Sham + Std diet	Immediately post-injury (1 hr, 6 hr, 24 hr, 7 days)	KD: 8.4% protein, 78.8% fat, 0.8% carbohydrate, 5% fiber, 3.8% ash; Standard diet: 18.6% protein, 6.2% fat, 59.8% carbohydrate, 4.5% fiber; 6.02% ash; fed *ad libitum*
Prins and Hovda (2009) *USA*	Random pre-clinical ($n = 7$)	CCI, Mod[a], NR	Pre-adolescent (PND-35); Adult (PND-70); *SD* rats (90)	KD	PND-35 sham + Std diet; PND-35 sham + KD; PND-35 TBI + Std diet; PND-70 sham + Std diet; PND-70 sham + KD	Immediately post-injury (7 days)	KD: 8.4% protein, 78.8% fat, 0.8% carbohydrate, 5% fiber; Standard diet: 18.6% protein, 6.2% fat, 59.8% carbohydrate, 4.5% fiber; fed *ad libitum*
Deng-Bryant et al. (2011) *USA*	Pre-clinical ($n = 8$)	CCI, Mod[a], NR	Pre-adolescent (PND-35); Adult (PND-70); *SD* rats (UC)	KD	PND-35 sham + Std diet; PND-35 sham + KD; PND-35 TBI + Std diet; PND-70 sham + Std diet; PND-70 sham + KD; PND-70 TBI + Std diet	Immediately post-injury (6 hr or 24 hr)	KD: 8.4% protein, 78.8% fat, 0.8% carbohydrate, 5% fiber; Standard diet: 18.6% protein, 6.2% fat, 59.8% carbohydrate, 4.5% fiber; fed *ad libitum*
Schwartzkroin et al. (2010) *USA*	Random pre-clinical ($n = 3$)	Lateral FPI, Mod, NR	PND 56; *SD* rats (55)	KD	Sham + Std diet; TBI + Std diet	Immediately post-injury (3 weeks)	KD: 8% protein, 79% fat (>29% saturated fats), 0.76% carbohydrates, 12% water/fiber/ash; fed *ad libitum*
Greco et al. (2016) *USA*	Random pre-clinical ($n = 6$)	CCI, Mod[c], 0%[c]	PND-35 ($n = 36$), PND-70 ($n = 18$); *SD* rats (54)	KD	PND-35 sham + Std diet; PND-35 TBI + Std diet; PND-70 sham + Std diet; PND-70 TBI + Std diet	Immediately post-injury (6 hr or 24 hr)	KD: 8.4% protein, 78.8% fat, 0.8% carbohydrate, 5% fiber; Standard diet: 18.6% protein, 6.2% fat, 59.8% carbohydrate, 4.5% fiber; fed *ad libitum*

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TABLE 3 (Continued)

Author (year) *country*	Animal study type (# of study groups)	Method of TBI delivery, TBI severity, mortality rate	Animal details (*N*)	Intervention	Controls	Initiation of intervention (duration of intervention)	Dosage
Hu, Wang, Jin, et al. (2009) *China*	Random pre-clinical ($n = 4$)	Feeney weight drop, UC, NR	130–140 g; *SD* rats (80)	KD	Sham + Std diet; Sham + KD; TBI + Std diet	Immediately post-injury (72 hr)	KD: protein 17.4%, fat 69.8%, carbohydrate 0%; fed *ad libitum*
Hu, Wang, Qiao, et al. (2009) *China*	Random pre-clinical ($n = 5$)	Feeney weight drop, UC, NR	PND 35; *SD* rats (25)	KD	Sham + Std diet; Sham + KD; TBI + Std diet	Immediately post-injury (72 hr)	KD: protein 17.4%, fat 69.8%, carbohydrate 0%; fed *ad libitum*
Multi-supplement							
Wu et al. (2014) *USA*	Pre-clinical ($n = 5$)	FPI, Mod, NR	200–240 g; *SD* rats (UC)	Curcumin-enriched diet, DHA-enriched diet, or curcumin + DHA-enriched diet	Sham + Std diet; TBI + Std diet	Immediately post-injury (14 days)	Curcumin: 500 ppm enriched chow; DHA: 1.2% DHA enriched chow; fed *ad libitum*
Thau-Zuchman et al. (2019) *UK*	Random pre-clinical ($n = 3$)	CCI, Mod[c], 0%[c]	PND-70 to PND-84; 22–27 g; C57BL/J6 mice (30)	Fortasyn Connect multi-supplement enriched diet	Sham + Std diet; TBI + Std diet	Immediately post-injury (10 weeks)	Fed *ad libitum*
Polyunsaturated fatty acids							
Wu et al. (2011) *USA*	Pre-clinical ($n = 3$)	FPI, Mild, NR	200–240 g; *SD* rats (36)	DHA-enriched diet	Sham + Std diet; TBI + Std diet	Immediately post-injury (12 days)	1.2% DHA enriched chow; fed *ad libitum*
Su et al. (2016) *China*	Pre-clinical ($n = 4$)[b]	Feeney weight drop, Mod, 3.7%	250–300 g; *SD* rats (101[b])	Moderate (1:5) or high (1:1) ω-3/ω-6 ratio PUFA oil via gavage	Sham + "western" diet (low ω-3/ω-6 PUFA ratio; 1:30); TBI + "western" diet	Immediately post-injury then 1 dose per 24 hr until sacrifice (72 hr, 5 days, 7 days, or 19 days)	All animals fed same fat-free chow and 5.5 ml/kg PUFA oil mixture: Low ratio − 4% fish oil + 96% linoleic acid; moderate ratio: 21% fish oil + 79% linoleic acid; or High ratio: 58% fish oil + 42% linoleic acid
Shin and Dixon (2011) *USA*	Pre-clinical ($n = 4$)	CCI, Mod to severe[c], 0%	~PND-60[c]; 275–300 g; *SD* rats (~20to 24[c])	Fish oil supp via gavage	Sham + olive oil; sham	Immediately post-injury then 1 dose per 24 hr until sacrifice (7 days)	1.5 ml/day containing 360 mg EPA & 240 mg DHA
Schober et al. (2016) *USA*	Pre-clinical ($n = 3$)	CCI, Mod to severe[a], 1.5%–3.0% across groups	Immature; PND17; *SD* rats (400)	DHA-enriched diet	Sham + Std diet; TBI + Std diet	Immediately post-injury (24 hr, 48 hr, 72 hr, or 50 days)	0.1% DHA enriched chow; fed *ad libitum*

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TABLE 3 (Continued)

Author (year) *country*	Animal study type (# of study groups)	Method of TBI delivery, TBI severity, mortality rate	Animal details (*N*)	Intervention	Controls	Initiation of intervention (duration of intervention)	Dosage
Bailes and Mills (2010) *USA*	Pre-clinical ($n = 4$)	MIAI, Severe[a], 0%	Adult; 350–400 g; *SD* rats (40)	Low or high DHA-enriched diet	Sham + Std diet; TBI + Std diet	Immediately post-injury (30 days)	Low DHA: 10 $mg^{-1}kg^{-1}day$; high DHA: 40 $mg^{-1}kg^{-1}day$; fed *ad libitum*
Mills et al. (2011) *USA*	Pre-clinical ($n = 4$)	MIAI, Severe, 0%	Adult; 350–400 g; *SD* rats (40)	Low or high fish oil (EPA + DHA) supp via gavage	Sham + Std diet; TBI + Std diet	Initiated 24 hr post-injury then 1 dose per 24 hr until sacrifice (30 days)	Low fish oil: 10 $mg^{-1}kg^{-1}day$; high fish oil: 40 $mg^{-1}kg^{-1}day$
Zhu et al. (2017) *China*	Random pre-clinical ($n = 4$)	FPI, UC, NR	PND-49; 300–500 g; *SD* rats; 40 male, 40 female (80)	Low or high DHA supp via gavage	Sham + Std diet; TBI + Std diet	First dose 30 min post-injury then 1 dose per 24 hr until sacrifice (15 days)	Low DHA: 370 $mg^{-1}kg^{-1}day$; high DHA: 740 $mg^{-1}kg^{-1}day$
Traditional eastern medicine							
Özevren et al. (2018) *Turkey*	Pre-clinical ($n = 3$)	MIAI, Mild, 0%	280–330 g; *SD* rats (36)	Ganoderma lucidum supp via gavage	Sham + saline vehicle; TBI + saline vehicle	First dose 30 min post-injury (7 days)	20 $ml^{-1}kg^{-1}day$
Sharma et al. (2010) *USA*	Random pre-clinical ($n = 4$)	FPI, Mod, NR	~PND-60; *SD* rats (24)	Curcumin-enriched diet	Sham + Std diet; sham + curcumin-enriched diet; TBI + Std diet;	Immediately post-injury (14 days)	Chow enriched with 500 ppm of curcumin; fed *ad libitum*
Wang, Cui, et al. (2016) *China*	Random pre-clinical ($n = 4$)	CCI, Mod to severe[a], ~10%	PND-56 to PND-70; 200–250 g; *SD* rats (96)	HYSA supp via gavage in low and high dosage	Sham; TBI + saline vehicle	Dose ~20 min post-injury (Single dose post-injury)	Low HSYA: 10 mg/kg; high HSYA: 30 mg/HSYA
Wang, Li, et al. (2016) *China*	Random pre-clinical ($n = 3$)	CCI, Mod to severe[a], 10%	Adult; 220–280 g; *SD* rats (88)	RZD supp via gavage	Sham; TBI + vehicle	First dose 4 hr post-injury then one dose per 24 hr until sacrifice (14 or 24 days)	20 $mg^{-1}kg^{-1}day$
Xing et al. (2016) *China*	Random pre-clinical ($n = 6$)	CCI, Mod to severe[a], NR	200–250 g; *SD* rats (182)	XFZY supp via gavage in low and high dosage	Sham + saline vehicle; TBI + saline vehicle; sham + low XFZY dose; sham + high XFZY dose	First dose immediately post-injury then 1 dose per 24 hr until sacrifice (24 hr, 72 hr, 7 days, 14 days, 21 days)	Low XFZY: 9 g/kg; high XFZY: 18 g/kg
Xu et al. (2017) *China*	Random pre-clinical ($n = 6$)	CCI, Mod to severe[a], NR	200–300 g; *SD* rats (108)	Rhubarb (low, moderate, high) or rhein (single dose) supp via gavage	Sham; TBI + vehicle	Immediately post-injury (8, 12, 24 hr)	Low rhubarb: 3 g/kg; moderate rhubarb: 6 g/kg; high rhubarb: 9 g/kg; Rhein: 12 mg/kg

(Continues)

TABLE 3 (Continued)

Author (year) *country*	Animal study type (# of study groups)	Method of TBI delivery, TBI severity, mortality rate	Animal details (*N*)	Intervention	Controls	Initiation of intervention (duration of intervention)	Dosage
Xie et al. (2018) *China*	Random pre-clinical ($n = 3$)	CCI, Mod to severe[a], NR	PND-42 to PND-56; 220–250 g; *SD* rats (15)	AR-RAS herbal formula supp via gavage	Sham + saline vehicle; TBI + saline vehicle	First dose ~45 min post-injury then 1 dose per 24 hr until sacrifice (14 days)	3.24 $g^{-1}kg^{-1}day$
Kumar et al. (2014) *India*	Random pre-clinical ($n = 5$)[b]	MIAI, Severe[a], NR	Adult; 250–300 g; Wistar rats (50[b])	Panax ginseng suspended in CMC via oral route	Sham + CMC vehicle; TBI + CMC vehicle	Initiated 14 days post-injury (14 days)	Panax ginseng: 0.5 ml/100 g of bodyweight/day; suspended in CMC delivered via oral route
Wang et al. (2018) China	Random pre-clinical ($n = 3$)	MIAI x 3, Severe, NR	PND70 to PND-77; 260–300 g; *SD* rats (30)	Berberine supp via gavage	Sham + saline vehicle; TBI + saline vehicle	First dose 24 hr post-injury then 1 dose per 24 hr until sacrifice (4 weeks)	200 mg/kg of bodyweight/day
Zhao et al. (2014) *China*	Random pre-clinical ($n = 5$)	Feeney weight drop, UC, NR	250–280 g; *SD* rats (50)	MSD supp via gavage in low, moderate, and high dosage	Sham + distilled water; TBI + distilled water	First dose 6 hr post-injury then 2 doses per 24 hr until sacrifice (24 hr, 72 hr, 5 days, 14 days)	Low MSD: 0.5 ml/200 g; moderate MSD: 1.0 ml/200 g; high MSD: 2.0 ml/200 g

[a]Inferred based on available information and criteria summarized by (Ma et al., 2019; Siebold et al., 2018).

[b]Additional groups and were present in study but were excluded due to being outside scope of review.

[c]Information acquired by contacting corresponding author.

Abbreviations: Mod, moderate TBI; NR, not reported in published article and not obtained by contacting author; supp, supplementation; Std, standard; UC, unclear in published article and not obtained by contacting author.

TABLE 4 Summary of biomarkers assessed and neurophysiological outcomes

	Intervention specifics	Biomarkers measured	Neurophysiological outcome evaluated		Brief summary of results and main takeaways
Anti-oxidants					
Toklu et al. (2009)	α-lipoic acid (ALA) delivered via gavage	Evans blue extravasation, brain water content	BBB integrity	↑	ALA ↓ oxidative stress, ↓ BBB disruption, and ↓ immune response versus control @ 48 hr post-injury
		Luminol and lucigenin chemiluminescence, TBARS, GSH, MPO	Oxidative stress	↓	
		Na-K-ATPase activity	Cellular energy imbalance	↓	
		TNF-α, IL-1β	Immune response	↓	
Itoh et al. (2013)	EGCG dissolved in drinking water	8-OHdG, 4-HNE positive cells; and MDA levels	Oxidative stress	↓	EGCG ↓ oxidative stress and ↓ apoptosis versus control @ pid 1 and 3; EGCG ↓ glial activation versus control @ pid 7
		NeuN, ssDNA, Bcl-2 positive cells	Morphological changes and apoptosis	MIX	
		GFAP positive cells	Glial activation	↓	
Ozbal et al. (2015)	α-Lipoic acid (ALA) delivered via gavage in low and high dose	Neuron density; caspase-3, and TUNEL positive cells	Morphological changes and apoptosis	↓	ALA ↓ morphological changes and apoptosis versus control in the cortex and hippocampus; ALA ↓ oxidative stress versus control @ 48 hr post-injury; benefit limited to cortex; greater benefits associated with higher dosage
		GPx, SOD, and MDA levels	Oxidative stress	↓	
Wei et al. (2015)	α-lipoic acid (ALA) delivered via gavage	Caspase-3, Cytochrome C, Bax expression; Nissl body staining, TUNEL positive cells	Morphological changes and apoptosis	↓	ALA ↓ morphological changes and apoptosis, ↓ oxidative stress, and ↓ edema versus control @ 48 hr post-injury
		MDA and GPx activity	Oxidative stress	↓	
		Brain water content	BBB integrity	↑	
Cheng et al. (2016)	(-)-Epicatechin supplementation delivered via gavage in low, moderate, high dose	Fluoro-jade, Nissl body and propidium iodide staining; TUNEL positive cells	Morphological changes and apoptosis	↓	(-)-Epicatechin ↓ morphological changes and apoptosis, ↓ oxidative stress, and ↓ edema @ pid 3; ↓ myelin damage versus control @ pid 28; greater benefits associated with higher dosage within acute phase; dosing not compared for all outcomes
		Brain water content	BBB integrity	↑	
		MPO, HO-1, oxidized hydroethidine, Perls staining	Oxidative stress	↓	
		MBP, Luxol fast blue staining; MMP-2 and MMP-9 activity	Cell membrane homeostasis	↑	
Ji et al. (2017)	Astaxanthin diluted in olive oil delivered via gavage	Lesion volume, cell density (mm^3)	Morphological changes and apoptosis	↓	Astaxanthin ↓ lesion volume, ↑ cell density and ↑ markers of plasticity, neurotransmission, and neurogenesis astaxanthin versus control @ pid 7
		Synapsin, GAP43, SYP, BDNF	Plasticity, neurotransmission, and neurogenesis	↑	

(Continues)

TABLE 4 (Continued)

	Intervention specifics	Biomarkers measured	Neurophysiological outcome evaluated		Brief summary of results and main takeaways
Jiang et al. (2017)	Catechin supplementation delivered via gavage	Brain infarction volume	Morphological changes and apoptosis	↓	Catechin ↓ infarction volume, ↓ BBB disruption, ↓ immune response versus control @ 24 hr post-injury; greater benefit associated with higher dosages
		Brain water content, Evans blue extravasation, occludin, ZO-1	BBB integrity	↑	
		IL-1β, iNOS, IL-6, arginase	Immune response	↓	
Krishna et al. (2019)	5% Blueberry-enriched diet	BDNF, CREB, and CaMKII	Plasticity, neurotransmission, and neurogenesis	↑	Blueberry-enriched diet ↓ oxidative stress versus control; blueberry ↑ markers of plasticity versus control @ ~ pid 22; these ↑ were associated with improved behavioral outcomes
		4-HNE	Oxidative stress	↓	
Branched chain amino acids					
Cole et al. (2010)	Tap water containing valine, leucine, and isoleucine; or tap water containing phenylalanine	BCAA concentrations, net synaptic efficacy, Glutamate, GABA, BCATc, BCATm, BCKD, GAD, GDH, AAT1, AAT2	Plasticity, neurotransmission, and neurogenesis	↑	LIV BCAAs ↑ net synaptic efficacy versus control @ pid 7; TBI ↓ BCAA transanimation and enzymes responsible for glutamate metabolism
Lim et al. (2013)	Tap water containing valine, leucine, and isoleucine	Orexin activated neurons	Plasticity, neurotransmission, and neurogenesis	↑	BCAAs ↑ orexin activated neurons versus control @ pid 28, restoring regulation of arousal and wakefulness
Elliott et al. (2018)	Tap water containing valine, leucine, and isoleucine	Glutamate and GABA labeling	Plasticity, neurotransmission, and neurogenesis	↑	BCAA ↑ excitatory signaling in presynaptic terminals of hypothalamus and ↓ excitatory signaling in presynaptic terminals of cortex versus control @ pid 7; no difference in inhibitory signaling in hypothalamus or cortex
Creatine					
Saraiva et al. (2012)	Creatine supplementation delivered via gavage	TBARS levels, protein carbonylation	Oxidative stress	↓	Creatine ↓ oxidative stress versus control @ pid 4 and 8
		Na+ -K+ ATPase activity	Cellular energy imbalance	NC	
Gerbatin et al. (2019)	Creatine supplementation delivered via gavage	Cell loss	Morphological changes and apoptosis	↓	↓ cell loss within hippocampus and ↑ inhibitory action creatine versus control @ pid 35
		GABAergic inhibitory neurons, GAD, GAD67, and [3H]flunitrazepam binding	Plasticity, neurotransmission, and neurogenesis	↑	

(Continues)

TABLE 4 (Continued)

	Intervention specifics	Biomarkers measured	Neurophysiological outcome evaluated		Brief summary of results and main takeaways
Fasting and caloric restriction					
Davis et al. (2008)	Fasting	Tissue sparing	Morphological changes and apoptosis	MIX	24 hr fast ↑ tissue sparing and ↓ oxidative stress versus control @ 24 hr post moderate TBI; no differences in tissue sparing 24 hr fast post severe TBI; nor 48 hr fast @ 48 hr post moderate or severe TBI
		Ca^2+ load and mitochondrial complex function	Cellular energy imbalance	↓	
		ROS production, protein carbonyls, and lipid peroxidation	Oxidative stress	↓	
Liu et al. (2017)	Caloric restriction	Nissl bodies	Morphological changes and apoptosis	↓	Caloric restriction ↑ autophagy, ↓ glial activation, ↑ cell density compared to control and high energy group @ pid 36
		GFAP positive cells	Glial activation	↓	
		mTOR, LC3B and Beclin-1 positive cells	Immune response	↑	
Rubovitch et al. (2019)	Intermittent fasting or caloric restriction	SIRT1 expression	Cellular energy imbalance	MIX	Caloric restriction and intermittent fasting ↑ energy metabolism versus control @ pid 30 in cortex; only fasting ↑ energy metabolism versus control in hippocampus @ pid 30
Ketogenic diet					
Prins et al. (2005)	KD	Fluoro-jade staining, contusion volume, and neuronal preservation	Morphological changes and apoptosis	MIX	KD ↓ cellular degeneration versus control @ 6 and 24 hr post-injury; and ↓ contusion volume versus control @ pid 7, benefits were specific to the pre-adolescent and adolescent animals
		Plasma glucose, lactate, and βOHB levels	Cellular energy imbalance	MIX	
Hu, Wang, Jin, et al. (2009)	KD	TUNEL positive cells, caspase-3 positive cells, cytosolic cytochrome c release, and mitochondrial cytochrome c release	Morphological changes and apoptosis	↓	KD ↓ apoptosis, ↓ mitochondrial dysfunction, and ↓ edema versus control @ 72 hr post-injury
		Plasma glucose and βOHB levels	Cellular energy imbalance	↓	
		Brain water content	BBB integrity	↑	
Hu, Wang, Qiao, et al. (2009)	KD	TUNEL positive cells, Bax mRNA, and Bcl-2 mRNA	Morphological changes and apoptosis	↓	KD ↓ apoptosis and ↓ edema versus control @ 72 hr post-injury
		Plasma βOHB levels	Cellular energy imbalance	↓	
		Brain water content	BBB integrity	↑	
Prins and Hovda (2009)	KD	Contusion volume	Morphological changes and apoptosis	MIX	KD ↓ contusion volume and ↓ cerebral metabolic rates of glucose in ipsilateral cortex, hippocampus, and thalamus @ pid 1, 3, and 7, benefits limited to younger animals
		Cerebral metabolic rates for glucose; plasma glucose, lactate, and βOHB levels	Cellular energy imbalance	MIX	

(Continues)

TABLE 4 (Continued)

	Intervention specifics	Biomarkers measured	Neurophysiological outcome evaluated		Brief summary of results and main takeaways
Schwartzkroin et al. (2010)	KD	Cell counts; dorsal hippocampal volume	Morphological changes and apoptosis	NC	No difference cell loss KD versus control @ pid 63; KD ↓ amount of astrogliosis and microgliosis versus control @ pid 63
		Hippocampal astrogliosis and microgliosis	Glial activation	↓	
Deng-Bryant et al. (2011)	KD	Plasma glucose, lactate, βOHB levels; nuclear magnetic resonance spectroscopy to quantify metabolites within brain: ATP, creatine, phosphocreatine, GABA, glutamate, glutamine, choline, taurine, glycine, myo-inositol, aspartate, alanine, NAA, lactate, PEtn, PChol, GroPEtn, GroP-Chol, and NAD	Cellular energy imbalance	MIX	Mixed results of KD on energy metabolites versus control; results were age and time post-injury specific; broadly, KD ↓ metabolic deficits in younger animals versus control
Greco et al. (2016)	KD	3NT, 4-HNE, SOD1, SOD2, and NQO1	Oxidative stress	MIX	KD ↓ oxidative stress versus control. Benefits varied between 6–24 hr post-injury, and were limited to younger animals
		Mitochondrial complex function	Cellular energy imbalance	MIX	
Zhang et al. (2018)	KD	Plasma βOHB levels; NAA:creatine ratio and choline:creatine ratio	Cellular energy imbalance	MIX	Mixed results of KD on energy metabolism versus control @ pid 7; no difference in edema between all groups; ↑ autophagy KD versus control @ pid 7
		Brain edema	BBB integrity	NC	
		Beclin-1 expression	Immune response	↑	
Multi-supplement					
Wu et al. (2014)	Curcumin-enriched diet, DHA-enriched diet, or curcumin + DHA-enriched diet	BDNF and p-TrkB	Plasticity, neurotransmission, and neurogenesis	↑	DHA and curcumin (in isolation and combination) ↓ oxidative stress, ↑ cell membrane homeostasis, and ↑ markers of plasticity versus control @ pid 14; combination of DHA and curcumin elicited greater benefits than either in isolation
		4-HNE and 4-HHE	Oxidative stress	↓	
		FADS2, 17β-HSD4, DHA content, *n*-3 DPA content, and serum cholesterol	Cell membrane homeostasis	↑	
Thau-Zuchman et al. (2019)	Fortasyn Connect multi-supplement enriched diet	Lesion size	Morphological changes and apoptosis	↓	Multi-supplement ↓ morphological changes and apoptosis, ↑ cell membrane homeostasis, ↓ glial activation, and ↑ markers of plasticity and neurogenesis versus control @ pid 70
		Iba-1, TSPO, GFAP, APC positive cells, and NogoA levels	Glial activation	↓	
		BrdU positive cells, DCX positive cells, synaptophysin, and β-APP levels	Plasticity, neurotransmission, and neurogenesis	↑	
		Plasma AA, EPA and DHA levels; MBP, phosphatidylcholine and phosphatidylethanolamine levels	Cell membrane homeostasis	↑	

(Continues)

TABLE 4 (Continued)

	Intervention specifics	Biomarkers measured	Neurophysiological outcome evaluated		Brief summary of results and main takeaways
Polyunsaturated fatty acids					
Bailes and Mills (2010)	Low or high DHA-enriched diet	Caspase-3 positive axons	Morphological changes and apoptosis	↓	Both low and high dose of DHA ↓ apoptosis, ↑ cell membrane homeostasis, and ↓ number of injured axons versus control @ pid 30; high dose DHA had greater benefit on membrane homeostasis than low dose
		Serum DHA and EPA levels; AA:EPA ratio	Cell membrane homeostasis	↑	
		β-APP-positive axons	Plasticity, neurotransmission, and neurogenesis	↑	
Shin and Dixon (2011)	Fish oil supplementation delivered via gavage	Dopamine release	Plasticity, neurotransmission, and neurogenesis	↑	Fish oil ↑ dopamine release versus control @ pid 7
Mills et al. (2011)	Low or high fish oil (EPA + DHA) supplementation delivered via gavage	Axons positive for active caspase-3 and cytochrome c	Morphological changes and apoptosis	MIX	Mixed results for influence of fish oil on apoptosis versus control @ pid 30; fish oil ↑ cell membrane homeostasis, and ↓ axonal damage versus control @ pid 30; no apparent differences between fish oil dosages
		AA:EPA ratio	Cell membrane homeostasis	↑	
		APP-positive axons; axons positive for active RMO-14	Plasticity, neurotransmission, and neurogenesis	↑	
Wu et al. (2011)	DHA-enriched diet	4-HNE, SOD, and SIR2 levels	Oxidative stress	↓	DHA ↓ oxidative stress and ↑ cell membrane homeostasis versus control @ ~ pid 7–12; DHA ↑ markers of plasticity to sham levels @ ~ pid 7–12
		Brain DHA content and iPLA2 levels	Cell membrane homeostasis	↑	
		BDNF, CAMKII, Syn-1, CREB, and STX-3 levels	Plasticity, neurotransmission, and neurogenesis	↑	
Schober et al. (2016)	DHA-enriched diet	TNF-α, IL-1B, CCL2, IL-6, IL-10, IL-2	Immune response	MIX	DHA ↑ tissue sparing @ pid 3 and 50, ↓ edema @ pid 12, and ↓ oxidative stress @ pid 1 within the cortex versus control; mixed results for MRI measures @ pid 12 and 28; mixed immune response DHA versus control @ pid 1 and 2
		NOx	Oxidative stress	↓	
		Tissue sparing and contusion volume	Morphological changes and apoptosis	↓	
		Edema	BBB integrity	↑	
		Fractional anisotropy, radial diffusivity, axial diffusivity, and tract volume measured by MRI	Plasticity, neurotransmission, and neurogenesis	MIX	
Su et al. (2016)	Moderate (1:5) or high (1:1) ω-3/ω-6 ratio PUFA oil delivered via gavage	Evans blue extravasation, edema; occludin and MFSD2A levels	BBB integrity	↑	High dose of ω-3 fatty acids ↓ oxidative stress and ↓ BBB disruption @ pid 5 versus "western diet" control; No benefit moderate dose of ω-3 fatty acids versus "western diet" control @ pid 5
		4-HNE	Oxidative stress	↓	

(Continues)

TABLE 4 (Continued)

	Intervention specifics	Biomarkers measured	Neurophysiological outcome evaluated		Brief summary of results and main takeaways
Zhu et al. (2017)	Low or high DHA supplementation delivered via gavage	Gross morphology; Bcl-2, Bax, and caspase-3 expression	Morphological changes and apoptosis	↓	Low and high dose of DHA ↓ morphological changes and apoptosis @ pid 15 versus control; high dose ↓ markers of apoptosis closer to sham levels than low dose
Traditional eastern medicine					
Sharma et al. (2010)	Curcumin-enriched diet	4-HNE levels	Oxidative stress	↓	Curcumin ↓ oxidative stress, ↑ cell membrane homeostasis, and ↑ markers of plasticity, neurotransmission, and neurogenesis versus control @ pid 15; these benefits were associated with improved behavioral outcomes
		iPLA2 and FATPs levels	Cell membrane homeostasis	↑	
		STX-3, GAP-43, and NR2B levels	Plasticity, neurotransmission, and neurogenesis	↑	
Kumar et al. (2014)	Panax ginseng suspended in CMC delivered via oral route in low, moderate, and high dosage	MDA, GSH, nitrite, catalase, and SOD levels	Oxidative stress	↓	Moderate and high dose of panax ginseng ↓ oxidative stress, ↓ impaired neurotransmission, and ↓ immune response within cortex and hippocampus versus control @ pid 28; no difference between low dose of panax ginseng versus control for outcomes
		Acetylcholinesterase levels	Plasticity, neurotransmission, and neurogenesis	↑	
		TNF-α and IL-6 levels	Immune response	↓	
Zhao et al. (2014)	Modified Shengyu decoction (MSD) supplementation delivered via gavage in low, moderate, and high dosage	Water content	BBB integrity	MIX	Both moderate and high dose of MSD ↓ cell loss in cortex and hippocampus @ pid 14; moderate dose MSD ↓ edema versus control @ pid 1, and ↓ glial activation @ pid 5 in cortex and hippocampus; mixed results of moderate dose MSD on immune response versus control @ pid 3; no doses led to a difference in contusion volume versus control @ pid 14
		Contusion volume and neuronal loss	Morphological changes and apoptosis	MIX	
		IL-1β, IL-6, TNF-α, and IL-10 levels	Immune response	MIX	
		GFAP and Iba-1 positive cells	Glial activation	MIX	
Wang, Cui, et al. (2016)	Hydroxysafflor yellow A (HYSA) supplementation delivered via gavage in low and high dosage	MDA, SOD, catalase levels; and GSH:GSSG ratio	Oxidative stress	↓	Both low and high dose HSYA ↓ oxidative stress versus control @ 6, 12, and 24 hr post-injury; high dose appeared to have greater benefit than low dose
Wang, Li, et al. (2016)	Rhizoma drynariae (RZD) supplementation delivered via gavage	Lesion volume	Morphological changes and apoptosis	↓	RZD ↓ lesion volume @ pid 3 versus control; and mixed results for immune response versus control
		Plasma IL-6 and IL-10 levels	Immune response	MIX	

(Continues)

TABLE 4 (Continued)

	Intervention specifics	Biomarkers measured	Neurophysiological outcome evaluated		Brief summary of results and main takeaways
Xing et al. (2016)	Xuefu Zhuyu decoction (XFZY) supplementation delivered via gavage in low and high dosage	AKT	Morphological changes and apoptosis	MIX	Low dose of XFZY ↓ phosphorylation of markers within the PI3K/AKT/mTOR signaling pathway, thereby collectively ↓ immune response and neuroinflammation versus control @ pid 1, 3, 7, and 14; Low dose XFZY ↑ cell membrane homeostasis versus control @ pid 1, 3, 7, and 14; mixed results for the high dose of XFZY versus control, overall low dose associated with better outcomes versus control
		mTOR	Cellular energy imbalance	MIX	
		p70S6K	Plasticity, neurotransmission, and neurogenesis	MIX	
		AA levels	Cell membrane homeostasis	MIX	
		TNF-α and IL-1β levels	Immune response	↓	
Xu et al. (2017)	Rhubarb (low, moderate, high) or rhein (single dose) supplementation delivered via gavage	SOD, catalase, MDA levels; GSH:GSSH ratio	Oxidative stress	↓	Rhubarb and rhein ↓ oxidative stress versus control @ 8, 16, 24 hr post-injury; greater benefits associated with higher dosages; similar benefit observed between high dose of rhubarb and dose of rhein
Özevren et al. (2018)	Ganoderma lucidum supplementation delivered via gavage	MDA, GSH, and MPO levels	Oxidative stress	↓	Ganoderma lucidum ↓ oxidative stress, ↓ BBB permeability, ↑ neurogenesis, and ↑ immune response versus control @ pid 7; no difference in apoptosis ganoderma lucidum versus control @ pid 7
		Brain water content and BBB permeability	BBB integrity	↑	
		CD68	Immune response	↑	
		Bcl-2	Morphological changes and apoptosis	NC	
		VEGF	Plasticity, neurotransmission, and neurogenesis	↑	
Wang et al. (2018)	Berberine supplementation delivered via gavage	Bax, cytochrome c, NF-κB, and p38 mAPK expression	Morphological changes and apoptosis	↓	Berberine ↓ apoptosis, ↓ immune response, and ↑ angiogenesis versus control @ pid 28
		VEGF expression	Plasticity, neurotransmission, and neurogenesis	↑	
		IL-1β, TNF-α, MCP-1, and ATF-2 expression	Immune response	↓	
Xie et al. (2018)	Astragali Radix and Radix Angelica Sinensis (AR-RAS) herbal formula supplementation delivered via gavage	NogoA expression	Glial activation	↓	AR-RAS ↓ glial activation versus control @ pid 14

Abbreviations: MIX, mixed results for biomarkers; NC, no change of biomarkers; ↓, reduction of biomarkers; ↑, increase of biomarkers.

3.3 | Nutritional interventions and neurophysiological outcomes

3.3.1 | Nutritional interventions

Nutritional interventions were administered to animals by supplementing a standard diet with a specific nutrient or natural compound, by directly manipulating macro/micronutrient constituents of the animal's diet, or by controlling availability of food (Table 3). Supplementation allowed for controlled and precise nutrient dosage to animals, while manipulating diet/water permitted animals to feed/drink *ad libitum* when food/water was available. Nutritional interventions described by included studies fell within one of eight distinct themes which were:

1. natural compounds with known anti-oxidant properties (Cheng et al., 2016; Itoh et al., 2013; Ji et al., 2017; Jiang et al., 2017; Krishna et al., 2019; Ozbal et al., 2015; Toklu et al., 2009; Wei et al., 2015);
2. branched chain amino acids (BCAA) (Cole et al., 2010; Elliott et al., 2018; Lim et al., 2013);
3. creatine (Gerbatin et al., 2019; Saraiva et al., 2012);
4. fasting and caloric restriction (Davis et al., 2008; Liu et al., 2017; Rubovitch et al., 2019);
5. KD (Deng-Bryant et al., 2011; Greco et al., 2016; Hu, Wang, Jin, et al., 2009; Hu, Wang, Qiao, et al., 2009; Prins et al., 2005; Prins & Hovda, 2009; Schwartzkroin et al., 2010; Zhang et al., 2018);
6. multi-supplements (Thau-Zuchman et al., 2019; Wu et al., 2014);
7. ω-3 polyunsaturated fatty acids (PUFAs) (Bailes & Mills, 2010; Mills et al., 2011; Schober et al., 2016; Shin & Dixon, 2011; Su et al., 2016; Wu et al., 2011; Zhu et al., 2017); or
8. natural compounds used in traditional eastern medicine (Kumar et al., 2014; Özevren et al., 2018; Sharma et al., 2010; Wang et al., 2018; Wang, Fan, et al., 2016; Wang, Zhang, et al., 2016; Xie et al., 2018; Xing et al., 2016; Zhao et al., 2014).

3.3.2 | Neurophysiological outcomes

Biomarkers of morphological changes and apoptosis (24 studies), plasticity, neurotransmission, and neurogenesis (18 studies), indicators of oxidative stress (18 studies), cellular energy imbalance (12 studies), cytokines representative of immune response post-TBI (11 studies), BBB integrity (11 studies), cell membrane homeostasis (8 studies), and glial activation (6 studies) were NP outcomes evaluated (Tables 4 and S1). Additionally, 29/43 studies included neurocognitive and/or behavioral outcome measures. Neurocognitive and behavioral outcomes were outside the focus of this review and are only discussed in subsequent sections if relevant. An overview of results for each study is available in Table S1.

3.3.3 | Anti-oxidants

Eight studies administered compounds with known anti-oxidant properties to animals by gavage (an orally inserted tube to administer food/supplement directly to stomach) or by enriching the animal's diet/drinking water with the compound. Anti-oxidant compounds α-lipoic acid (ALA) (Ozbal et al., 2015; Toklu et al., 2009; Wei et al., 2015), catechin (Jiang et al., 2017), (-)-epicatechin(Cheng et al., 2016), and astaxanthin (Ji et al., 2017) were delivered via oral gavage. In the remaining studies, animals received (–)-epigallocatechin gallate (EGCG) dissolved in drinking water (Itoh et al., 2013), and a diet enriched with blueberries (Krishna et al., 2019). In each study the intervention was initiated within 3 hr of TBI. In 7/8 anti-oxidant studies, delivered compounds were associated with decreased markers of oxidative stress versus control. Two studies reported reduced BBB disruption following ALA delivery. Both ALA and astaxanthin demonstrated capacity to attenuate morphological changes and apoptosis versus control post-TBI. Phenols (catechin and EGCG) elicited an anti-apoptotic benefit. Increased markers of plasticity were reported following a blueberry-enriched diet and astaxanthin supplementation versus control. Specifically, two doses of ALA after weight drop TBI reduced BBB disruption, apoptosis, and oxidative stress within the first 48 hr after injury, although longer term outcomes were not explored (Ozbal et al., 2015; Toklu et al., 2009; Wei et al., 2015). Collectively, animals gavaged with phenols (catechin and EGCG) beginning the same day as moderate to severe TBI displayed less apoptotic damage and oxidative stress and increased BBB integrity compared to controls (Cheng et al., 2016; Itoh et al., 2013; Jiang et al., 2017).

3.3.4 | Branched chain amino acids

Three studies provided tap water mixed with BCAAs valine, leucine, and isoleucine to be drank *ad libitum* by mice post-TBI (Cole et al., 2010; Elliott et al., 2018; Lim et al., 2013). Two studies provided BCAA infused water 48 hr post-injury while the third made BCAAs available immediately post-injury. Only biomarkers representative of neurotransmission were measured post-TBI; where administration of BCAAs (valine, leucine, and isoleucine dissolved in tap water and drank *ad libitum* beginning 48 hr after mild to moderate FPI and lasting for 5 days) improved synaptic efficacy (Cole et al., 2010; Elliott et al., 2018). These BCAA associated benefits supported the restoration of excitatory (glutamatergic) and inhibitory (GABAergic) neuron balance post-TBI. Greater excitatory–inhibitory balance was related to improved regulation of sleep and arousal/wakefulness versus control at 4 weeks post-FPI in two studies (Elliott et al., 2018; Lim et al., 2013).

3.3.5 | Creatine

Two studies interrogated the effect of creatine supplementation, delivered by oral gavage, on NP outcomes post-TBI (Gerbatin et al., 2019; Saraiva et al., 2012). Creatine reduced oxidative stress and cellular energy imbalance (Saraiva et al., 2012) and there was reduced cells lost within the hippocampus and increased inhibitory

neuron action versus control (Gerbatin et al., 2019). Increased inhibitory action associated with creatine supplementation also had a protective effect against drug-induced seizures (to simulate epileptic seizures post-TBI) versus control in one study (Gerbatin et al., 2019).

3.3.6 | Fasting and caloric restriction

Two studies investigated fasting and caloric restriction in isolation (Davis et al., 2008; Liu et al., 2017), while a third study evaluated both interventions to determine if one was more efficacious post-TBI (Rubovitch et al., 2019). Rats that were acutely fasted for 24 hr after induction of moderate TBI demonstrated increased tissue sparing along with reduced oxidative stress and cellular energy imbalance compared to controls (Davis et al., 2008). Tissue sparing was not observed at 48 hr following moderate TBI, nor at either timepoint for severe TBI. Data were not available for oxidative stress and cellular energy imbalance outcomes following 48 hr of fasting. Adult mice assigned to caloric restriction demonstrated reduced glial activation, preserved cell density, and increased autophagic activity post-TBI compared to controls (Liu et al., 2017). Mice assigned to a high energy diet (130% of normal caloric intake) did not demonstrate any of the same benefits as seen following caloric restriction (Liu et al., 2017). Both chronic intermittent fasting and caloric restriction (Table 3. shows specific parameters) improved neurometabolic outcomes in the cortex of mice with TBI 30 days post-injury. Only intermittent fasting produced this neurometabolic benefit within the hippocampus for TBI versus control (Rubovitch et al., 2019).

3.3.7 | Ketogenic diet

The KD represents the most researched NUT to attenuate secondary damage after TBI as it was reported for eight studies. In all studies, KD increased metabolism of β-hydroxybutyrate, reducing neuronal and glial reliance upon glucose as a primary fuel source. Four of eight KD studies compared effects of this diet post-TBI between pre-adolescent and adult rats (Deng-Bryant et al., 2011; Greco et al., 2016; Prins et al., 2005; Prins & Hovda, 2009). Following moderate TBI, adolescent rats receiving a KD demonstrated a reduction in cellular energy imbalances and markers of apoptosis (Deng-Bryant et al., 2011; Greco et al., 2016; Hu, Wang, Jin, et al., 2009; Hu, Wang, Qiao, et al., 2009; Prins et al., 2005; Prins & Hovda, 2009). However, these NP benefits did not appear to extend to adult animals. The remaining KD studies only measured post-TBI outcomes in adult rats and presented mixed results in regard to anti-apoptotic, preservation of BBB integrity, and mitochondrial energy metabolism (Hu, Wang, Jin, et al., 2009; Hu, Wang, Qiao, et al., 2009; Schwartzkroin et al., 2010; Zhang et al., 2018). While KD was associated with reduced glial activation versus control, this finding was not replicated across multiple studies for pre-adolescent or adult rats (Schwartzkroin et al., 2010).

3.3.8 | Multi-supplement

Two studies (Thau-Zuchman et al., 2019; Wu et al., 2014) provided multi-supplements as the intervention. Mice that were provided with 10 weeks of a multi-supplement enriched diet (Fortasyn® Connect—containing DHA, eicosapentaenoic acid, uridine monophosphate, choline, folic acid, vitamins B12, B6, C, and E, and selenium) exhibited reduced lesion size and glial activation compared to controls (Thau-Zuchman et al., 2019). Mice on the multi-supplement diet had improved cell membrane homeostasis and increased markers of plasticity and neurogenesis (Thau-Zuchman et al., 2019). While these positive outcomes associated with a Fortasyn® Connect enriched diet were encouraging, it was unclear which constituents within the supplement facilitated these outcomes. Both a curcumin-enriched diet and a DHA-enriched diet reduced oxidative stress, supported cell membrane homeostasis, and increased markers of plasticity post-TBI in rats compared to control at 2 weeks post-injury (Wu et al., 2014). All these benefits were observed to a greater extent when curcumin and DHA were combined within the same diet, suggesting an additive advantage of combining these supplements (Wu et al., 2014).

3.3.9 | ω-3 polyunsaturated fatty acids

Of seven studies investigating PUFAs, three studies provided rats with a DHA-enriched diet (Bailes & Mills, 2010; Schober et al., 2016; Wu et al., 2011) while the others delivered DHA (Zhu et al., 2017), fish oil (Mills et al., 2011; Shin & Dixon, 2011), or a mixed ω-3/ω-6 PUFA oil (Su et al., 2016) via gavage. Treatment with PUFAs was initiated immediately post-injury in six studies, with the remaining study delaying initiation until 24 hr post-injury (Mills et al., 2011). Delivery of ω-3 PUFAs demonstrated capacity to attenuate apoptosis and oxidative stress, while promoting cell membrane homeostasis and BBB integrity, and upregulate markers of plasticity across the TBI spectrum (Bailes & Mills, 2010; Mills et al., 2011; Schober et al., 2016; Su et al., 2016; Wu et al., 2011, 2014; Zhu et al., 2017). These ω-3 PUFA associated NP benefits between 3 and 50 days post-TBI followed both an enriched diet fed *ad libitum* or delivery via gavage. Delivery of DHA reduced post-TBI apoptosis in three (Bailes & Mills, 2010; Schober et al., 2016; Zhu et al., 2017) of four studies (Mills et al., 2011) evaluating this outcome. Furthermore, rats supplemented with 1:1 ω-3/ω-6 ratio PUFA oil exhibited reduced oxidative stress compared to control (Su et al., 2016), and following a DHA-enriched diet in two studies (Schober et al., 2016; Wu et al., 2011). Similarly, 1:1 ω-3/ω-6 ratio PUFA oil supplementation resulted in reduced BBB disruption (Su et al., 2016), and two studies (Bailes & Mills, 2010; Wu et al., 2011) showed a DHA-enriched diet assisted cell membrane homeostasis. Two studies observed improved neurotransmission due to a DHA-enriched diet or fish oil supplementation (Bailes & Mills, 2010; Shin & Dixon, 2011). DHA reduced the number of injured axons in two studies (Bailes & Mills, 2010; Mills et al., 2011), however, there were mixed results of a DHA-related benefit on neurotransmission measured by magnetic resonance imaging in one study (Schober et al., 2016). The potential influence of DHA/fish

oil dosing was considered in three studies (Bailes & Mills, 2010; Mills et al., 2011; Zhu et al., 2017); a low and high dose of DHA improved apoptosis (Bailes & Mills, 2010; Zhu et al., 2017) and cell membrane homeostasis while reducing axonal damage (Bailes & Mills, 2010; Mills et al., 2011) compared to control, with the higher dose demonstrating greater benefit than the low dose in two studies (Bailes & Mills, 2010; Zhu et al., 2017). In an experiment where ω-3/ω-6 ratios were compared, rats that received a high ratio (1:1) demonstrated reduced BBB disruption post-TBI compared to "western diet" (1:30) controls. In contrast, delivery of a moderate ω-3/ω-6 ratio (1:5) did not alter BBB disruption versus the same controls (Su et al., 2016).

3.3.10 | Traditional eastern medicine

Ten distinct traditional eastern compounds were examined for post-TBI utility, including: curcumin (Sharma et al., 2010), panax ginseng (Kumar et al., 2014), modified Shengyu decoction (MSD; multi-herbal supplement) (Zhao et al., 2014), Hydroxysafflor Yellow A (HYSA; flavonoid extracted from Safflower) (Wang, Zhang, et al., 2016), Xuefu Zhuyu decoction (multi-herbal supplement) (Xing et al., 2016), ganoderma lucidum (mushroom polysaccharides) (Özevren et al., 2018), berberine (compound within Barberry roots) (Wang et al., 2018), Astragali Radix and Radix Angelica Sinensis (AR-RAS; multi-herbal supplement) (Xie et al., 2018), rhubarb and rhein (an active compound within rhubarb) (Xu et al., 2017), and Rhizoma drynariae (RZD; an active compound with roots of Drynaria Fortunei) (Wang, Li, et al., 2016). Rats that fed *ad libitum* for 2 weeks on a curcumin-enriched diet, beginning immediately after moderate FPI, displayed reduced oxidative stress while markers of cell membrane homeostasis and neuroplasticity were amplified at 14 days post-injury (Sharma et al., 2010; Wu et al., 2014). Overall, the traditional eastern interventions demonstrated capacity to influence the multiple aspects of secondary injury post-TBI in a beneficial manner compared to control. Due to heterogeneity and lack of replication for 9/10 traditional eastern interventions, results were not summarized; however, for an overview of these benefits please see Tables 4 and S1.

4 | DISCUSSION

4.1 | State and limitations of the evidence

The purpose of this review was to consolidate available evidence for post-TBI NUTs and their associated effects on NP outcomes in both animal and human studies. The aim was to identify NUTs that demonstrated the most plausible "over-the-counter" potential to reduce NP dysfunction (at a cellular level) after TBI in a way that may reduce downstream deficits experienced by clinical patients. Our review revealed that no studies have evaluated NP outcomes post-TBI in response to a NUT in humans. Several post-TBI NUTs were investigated for efficacy on clinical outcomes only, since these studies did not provide insight into how the NUTs interacted with pathophysiological mechanisms of TBI they are beyond the scope of this review (Aquilani et al., 2005, 2008; Noguchi et al., 2017; Sakellaris et al., 2006, 2008; Theadom et al., 2012, 2013, 2018; Walter et al., 2017; Yang & Xu, 2007). Therefore, knowledge of how NUTs may promote favorable NP outcomes after TBI relies entirely on pre-clinical evidence. Animal studies provide valuable insight into the molecular underpinnings and safety of emerging interventions (Shultz et al., 2017). However, methodological inconsistencies between animal studies and clinical investigations often lead to failed translation (de Vries et al., 2014; Perel et al., 2007; Shultz et al., 2017). A main review finding was the number of methodological caveats (and their relation to the biofidelity and validity of the evidence) that need to be considered before interpreting the translational potential and salient findings of interventions reviewed. Biofidelity refers to "concordance between specific features of a given animal model and the human disease or condition being modeled" and "goes hand in hand with confirmation of experimental results across different animal models with clinical findings in humans (i.e., validity)" (Wojnarowicz et al., 2017, p. 8). Aspects of study design including characteristics of animals used, method of TBI induction, intervention parameters, and measurement of outcomes in many of the included studies threaten biofidelity.

4.1.1 | Animal characteristics

Males have typically accounted for a higher proportion of recorded TBIs than females in clinical practice, however, females have typically experienced worse symptom burden and longer recovery timelines than males (Gupte et al., 2019; Merritt et al., 2019; Solomito et al., 2018). Only one study within our review included both male and female animals—but no sex-related results were presented (Zhu et al., 2017). This male bias has been extensively reported across multiple disciplines and is particularly prevalent within neuroscience (Prendergast et al., 2014). Exclusion of female rodents was often justified by the assumption that female rodents demonstrate higher variability than males due to the estrous cycle (Prendergast et al., 2014). However, a 2014 review consolidated data from 293 articles and concluded that females were not more variable than males across a range of physiological, morphological, and behavioral measures (Prendergast et al., 2014). There is a need to ensure inclusion of females in future pre-clinical and clinical investigations to understand if sex differences exist and to increase the likelihood of translation and generalizability.

Neurophysiological outcomes across multiple maturational stages in response to a post-TBI NUT were only evaluated in four studies, all of which administered a KD (Deng-Bryant et al., 2011; Greco et al., 2016; Prins et al., 2005; Prins & Hovda, 2009). The beneficial effect associated with KD was limited to younger animals. Evidence suggests maturational differences in NP consequences and recovery post-TBI (Shrey et al., 2011). Therefore, interactions would likely be shared between maturational stage and influence of NUTs on NP outcomes after TBI. Expanded knowledge of such

interactions would contribute to identification of nutritional candidates likely to translate to clinical practice.

All the interventions investigated within this review were administered to rodents, and no investigations evaluated the benefit of the intervention across multiple species. Concordance of results across more than one animal species has been shown to increase the likelihood of translation to humans in pharmaceutical toxicity studies (Olson et al., 2000). While financial and logistical challenges may make adopting a multi-species methodology difficult, such efforts would inform the design of future RCTs that would potentially provide information that may benefit TBI patients sooner.

4.1.2 | TBI induction

In most real-world TBIs the head moves freely and results in a mild closed head injury (Hiskens et al., 2019; Wang, Cui, et al., 2016, for reviews). Most included studies performed craniotomy to deliver a traumatic force directly to exposed dura. Freedom of head movement was prevented or unclear during TBI modeling in many studies. In a clinical setting, patients rarely require anesthetic following TBI, yet for ethical reasons, nearly all studies anesthetized animals while TBI was modeled. Anesthetic has been reported to effect behavioral and NP outcomes following TBI and may produce artifacts that complicate the interpretation of study findings (Shultz et al., 2017; Wojnarowicz et al., 2017, for reviews). Therefore, differences in the type and level of anesthetics delivered between laboratories during TBI induction require consideration when interpreting study outcomes. Since these factors are inconsistent with clinical mTBI (representing 95% of all TBIs) there is a need to adopt next-generation TBI modeling techniques that more accurately replicate the injury conditions experienced by the bulk of clinical patients (Hiskens et al., 2019; Shultz et al., 2017). Pre-clinical studies evaluating the effect of a NUT following blast-related TBIs, commonly seen during military service, are needed.

Most of the evidence consolidated within this review has been gained from animal studies replicating conditions of moderate to severe TBI. While these animal models aim to serve as surrogates for clinical presentations of TBI, differences in criteria used to ascertain TBI severity in animal studies (i.e., cortical deformation or velocity) versus clinical practice (Glasgow Coma Score and neuroimaging findings) must be taken into account when considering potential translation of study findings. Given the differing severity of pathophysiology across the TBI spectrum, it remains to be seen whether an intervention that shows promise within one severity of TBI severity is beneficial in more/less severe cases (Dixon, 2017).

4.1.3 | Intervention parameters and outcome measurements

Animals were either fed *ad libitum* or gavaged to deliver the NUT in studies within this review. Animals fed *ad libitum* may be representative of humans prescribed a supplement or altered diet as an intervention following TBI; however, these methods of delivery may lead to high variability in the amount of nutrient/compound ingested across subjects. Additionally, adherence may be an issue in clinical populations if the prescribed diet is vastly different than the patient's habitual diet. On the other hand, gavage allows for precise dosing but is invasive and involves bypassing the early stages of digestion and absorption. Delivery of a supplement orally would be more representative of what would be viable for clinical patients with mTBI, while gavage replicates tube feeding that may be necessary in humans following moderate or severe TBI. Future research should investigate if differences in post-TBI outcomes exist if the same NUT is fed *ad libitum* or delivered via gavage.

Evidence from pharmaceutical studies show that discontinuity between timing and mode of drug administration in animal and clinical studies contribute to failed translation (Agoston, 2017; Mohamadpour et al., 2019). These shortcomings may be due to our limited understanding of physiological and pathological temporal differences between humans and rodents (Agoston, 2017). For example, the lifespan of a rat is highly accelerated to that of a human; with one rat day equating to ~27 human days, and ~13.7 rat days being comparable to one human year (Agoston, 2017). Based on these figures initiating a NUT 24 hr post-injury in a rat may be representative of ~21 days post-injury in humans. Measuring outcomes at 7 days post-TBI in rats could possibly be indicative of outcomes at 6 months for humans. Research is needed to elucidate the possible temporal discordance between rodent and human TBI pathophysiology to increase the likelihood of intervention translation from the laboratory to clinical practice. Future studies should consider delivering a NUT in separate groups of animals to compare NP outcomes under ideal conditions (i.e., immediately post-injury) and under delayed conditions that are clinically representative.

A distinct advantage of animal studies is the ability to collect invasive outcome measures that would be unethical and impractical to acquire in humans. However, a strong case has been presented that "pre-clinical researchers should also prioritize incorporating methods/outcomes that are applicable in both the experimental and clinical settings" (Shultz et al., 2017, p. 404). Most studies in this review involved biochemical assays on slices of brain tissue post-sacrifice to quantify NP biomarkers. While this provided an accurate post-mortem measurement of outcomes within the brain, it may not be representative of the amount of circulating biomarkers while the animal was still alive. Incorporation of blood biomarkers and neuroimaging in animal studies would expand understanding of the relationships shared between biomarkers measured pre- and post-sacrifice. Incorporation of biomarkers in animal studies would allow comparisons and cross-validation against the growing number of biomarkers that can be measured in human clinical populations (Shultz et al., 2017).

Taken together, the examples in this section illustrate methodological factors that limit the biofidelity of the available evidence for NUTs to improve NP outcomes post-TBI. These factors need to be carefully considered when interpreting study results. Researchers

must find ways to account for financial and logistical constraints in order to improve the biofidelity and validity of investigations in a manner that will benefit clinical patients with TBI.

4.2 | Risk of bias

There is difficulty with assessing RoB in systematic reviews of animal studies due to poor methodological reporting (de Vries et al., 2014; Hooijmans et al., 2014; Perel et al., 2007). Studies within this review were often missing (or did not clearly communicate) key methodological details, including: blinding procedures, severity of TBI modeled, mortality rate following TBI, age of animals used, sample size, number of animals used for each outcome measure, and whether animals were randomized for outcome measure assessment (Kilkenny et al., 2010; Landis et al., 2012). As a result, determination of RoB was limited without these key methodological details (Tables 2 and 3). In some cases, authors of the original studies may have assumed that the reader had prior knowledge of commonly used methodologies in TBI animal studies, and thus these details were not explicitly stated. For example, random selection of housing may not be possible in a TBI study because uninjured control animals may overpower the TBI animals in competition for food. To overcome this issue animals belonging to the same study groups may have been housed together. To enhance methodological transparency, it is recommended that future studies incorporate a figure/diagram that clearly depicts key aspects of study design as shown in some studies (Gerbatin et al., 2019; Itoh et al., 2013; Kumar et al., 2014; Saraiva et al., 2012; Schwartzkroin et al., 2010; Thau-Zuchman et al., 2019; Xing et al., 2016).

The quality of results reported was low in many studies where only simple figures with p values were published. Values or descriptive statistics for outcomes were rarely provided in tabular format or within text, preventing meta-analysis to evaluate the size and meaningfulness of effects attributed to the delivered NUT. However, all studies reported a positive benefit of the NUT administered on NP outcomes compared to control. The absence of negative findings may be indicative of potential publication bias, possibly skewing the NUT associated benefits reported. Registration of animal studies to prevent publication bias, innovation of TBI models to improve biofidelity, thorough and transparent reporting of methodologies and results, and clinically relevant intervention timing and delivery are the focus of ongoing initiatives (Collins & Tabak, 2014; Hiskens et al., 2019; Hooijmans et al., 2012, 2014; Kilkenny et al., 2010; Landis et al., 2012; Mohamadpour et al., 2019; Wojnarowicz et al., 2017).

4.3 | Implications for clinical TBI patients

Unfortunately, due to limitations of the evidence, this review could not definitively recommend a single NUT as the primary "over-the-counter" candidate for clinical patients post-TBI. Further research should focus on anti-oxidant compounds (ALA, curcumin, phenols), BCAAs (combined leucine, isoleucine, valine), and ω-3 PUFAs (specifically DHA) which appear to be the most promising supplementation candidates that might facilitate improved clinical outcomes for TBI patients in the future.

Following TBI, patients often endure an array of functional and neurobehavioral deficits which seemingly develop as consequences of cellular damage and dysfunction triggered by the secondary injury phase of TBI (Giza & Hovda, 2014; Kenzie et al., 2018). Functional consequences of TBI often include mood instability, impaired cognition and memory, confusion, intolerance to cognitive and physical loading, vestibulo-ocular deficiencies, and sleep disturbances (Akin et al., 2017; Ellis et al., 2016; Kenzie et al., 2018; Mathias & Alvaro, 2012; Polinder et al., 2018; Theadom et al., 2016). Cellular disruptions impair neurological networks and subsequently manifest in symptom complaints and deficits at the experiential and social levels (Kenzie et al., 2018). Approximately 50% of patients experience sleep-wake disturbances after TBI (Mathias & Alvaro, 2012). Excessive glutamate release post-TBI creates an imbalance in the glutamate/GABA pool and contributes to impaired neurotransmission which in turn dysregulates networks responsible for restorative sleep (Kenzie et al., 2018). Without restorative sleep the patient may experience impaired executive function, mood instability, and high levels of stress that further compound sleep-wake disruption (Kenzie et al., 2018). In this regard, pre-clinical evidence suggests patients with post-TBI sleep-wake disorders may experience a positive benefit from BCAA supplementation via improved balance of glutamate/GABA pools within orexin neurons (Cole et al., 2010; Elliott et al., 2018; Lim et al., 2013).

Ionic dysregulation and subsequent mitochondrial dysfunction are hallmarks of TBI that contribute to oxidative stress (Giza & Hovda, 2014; Shichiri, 2014). Excessive free radical production can trigger apoptosis and lipid peroxidation of cell membranes (Giza & Hovda, 2014; Kannan & Jain, 2000; Stoica & Faden, 2010). Moderate and severe TBI can elicit considerable amounts of neuronal death severely impairing neuroconnectivity and transmission (Giza & Hovda, 2014; Kenzie et al., 2018). Across the TBI spectrum, mitochondrial dysfunction and impaired cell membrane homeostasis within neuronal, axonal, and glial cells can exacerbate neurotransmission impairment. Biomechanical forces deforming brain cells during TBI can damage axons and increase BBB permeability, both of which can be further aggravated by unregulated free radicals (Kuriakose et al., 2019; Ljubisavljevic, 2016). Compromised tight junctions between endothelial cells within the BBB results in cerebral edema further compromising neurotransmission (Kenzie et al., 2018; Luissint et al., 2012). Globally impaired neurotransmission can affect TBI patients through diminished sensorimotor integration, executive function, and working memory while manifesting clinically as mood instability, cognitive fatigue, and inability to complete activities of daily living (Kenzie et al., 2018). Introduction of anti-oxidants such as ALA, curcumin, or phenols early after moderate or severe TBI may promote tissue sparing and combat oxidative stress to blunt the overall cellular damage and downstream

impairments experienced by the patient (Cheng et al., 2016; Itoh et al., 2013; Jiang et al., 2017; Ozbal et al., 2015; Toklu et al., 2009; Wei et al., 2015). ω-3 PUFAs have demonstrated the same anti-apoptotic and anti-oxidant benefits as anti-oxidant compounds but with additional advantages (Lewis, 2016; Michael-Titus & Priestley, 2014). DHA is a major constituent of cell membranes within the central nervous system (Lo Van et al., 2016). At a cellular level, delivery of DHA post-TBI may proactively combat oxidative stress while providing the necessary building blocks to repair phospholipid bilayers damaged by lipid peroxidation. Pre-clinical evidence suggests that the administration of DHA after TBI upregulates brain-derived neurotrophic factor (BDNF) expression. Expression of BDNF plays a crucial role in the regulation of neuroplasticity and neurogenesis so that injured cells/networks can repair and/or reorganize themselves (Binder & Scharfman, 2004; Hempstead, 2015). Upregulation of BDNF by DHA supplementation (or other means) creates an internal environment that promotes recovery at the cellular and network level that may further alleviate functional deficits and symptom burden for patients. A pre-clinical study demonstrated that combining curcumin with DHA led to an additive benefit that exceeded the benefits observed following administration of either compound in isolation (Wu et al., 2014). There is a need to better understand how constituents of multi-supplement interact with outcomes.

Outside of the neurotrauma literature, reviews of NUTs to improve outcomes following musculoskeletal injuries and soft-tissue wounds have concluded that evidence supporting a single intervention in humans remains elusive (Quain & Khardori, 2015; Tipton, 2015; Wild et al., 2010). These reviews recommended a well-balanced diet of whole foods that are minimally processed and abstaining from alcohol consumption (Quain & Khardori, 2015; Tipton, 2015). Supplementation is likely only appropriate if the individual's habitual diet is deficient in a given nutrient or compound (Quain & Khardori, 2015; Tipton, 2015). Physiological responses to injury such as inflammation and apoptosis are important biological processes for recovery under normal conditions and complete elimination of these mechanisms would be unfavorable (Tipton, 2015). These general recommendations appear appropriate for patients with TBI in the interim while the biofidelity and validity of NUTs for TBI continue to be elucidated.

4.4 | Future directions

Modification of lifestyle factors, such as diet and exercise, are considered safe for investigation in human subjects given contraindications are considered and accounted for. This presents a unique opportunity in the case of NUTs for TBI to potentially conduct pre-clinical and clinical studies in parallel to accelerate the identification of strategies that might benefit clinical patients. Such study designs have begun to be adopted in other areas of translational research and serve as an innovative approach to account for the innate ethical and logistical limitations of both clinical and pre-clinical study designs (Jordan et al., 2019). Although studies evaluating NUTs have been conducted in humans with TBI, none were included in this review due to a lack of NP outcome measures. Future clinical investigations of post-TBI NUTs should make efforts to include NP measures within their outcome batteries. Due to the difficulties of running RCTs, it is imperative to include NP measures alongside clinical/behavioral measures in order to maximize the data acquired during a given collection. Inclusion of NP measures in human trials would improve our understanding of why interventions evaluated in RCTs fail or succeed, while providing cross-validation of biomarkers acquired in pre-clinical studies. Preliminary evidence suggests a positive effect of delivering exercise and DHA in combination after TBI on NP outcomes (Wu et al., 2013). Given exercise has become a pillar of TBI rehabilitation, future investigation into the relationship of exercise and NUTs is warranted. Finally, pre-clinical studies investigating diets/supplements that may be detrimental for post-TBI NP outcomes would be highly informative.

5 | CONCLUSIONS

Our objective was to identify NUTs introduced post-TBI demonstrating potential to improve NP outcomes after TBI. Available evidence regarding the efficacy of NUTs delivered to attenuate NP outcomes secondary to TBI was from 43 pre-clinical animal studies utilizing 2,897 rodents. No studies evaluated the effect of a NUT on NP outcomes of TBI in humans. The overall reporting of methods and results of included pre-clinical studies was poor, limiting the biofidelity of evidence. Decisive recommendations about which NUTs most effectively combat secondary injury following TBI in a manner that would benefit clinical patients could not be made. Initial evidence from animal studies provides a platform from which future investigations can be launched to determine which aspects of nutrition (particularly anti-oxidant compounds, BCAAs, and ω-3 PUFAs) could be manipulated to promote better recovery outcomes across the TBI spectrum for humans. With TBI complexity and heterogeneity of outcomes, innovative and collaborative efforts are needed for the identification of interventions to reduce the global health burden of this injury.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, J.M, P.H., K.Q., A.T., R.B.; *Methodology*, J.M, P.H., K.Q., A.T., R.B.; *Investigation*, J.M.; *Formal Analysis*, J.M., P.H.; *Writing - Original Draft*, J.M.; *Writing - Review & Editing*, J.M, P.H., K.Q., A.T., R.B.; *Supervision*, P.H., K.Q., A.T.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

TABLE S1 Expanded outcomes

TABLE S2 Abbreviation glossary

Transparent Peer Review Report

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