IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES
ISSN PRINT 2319 1775 Online 2320 7876
 Journal UGC CARE Listed (Group-I) Volume 10, Issue 11 2021

Role of Antioxidant-Rich Diets in Cognitive and Motor Recovery Following Traumatic Brain Injury

Maman Paul

Assistant Professor, Department of Physiotherapy, Guru Nanak Dev University, Amritsar-143005, Punjab, India

(e-mail: mamanpaul@gmail.com)

Abstract: Traumatic brain injury (TBI) represents a leading source of chronic neurological disability, frequently leading to deficits in memory, attention, cognition, coordination, and motor function. Rehabilitation programs aim to restore functional independence, but oxidative stress remains a major barrier to neuronal recovery and plasticity. Traumatic brain injury (TBI) and other forms of neurological trauma are strongly associated with oxidative stress, a condition in which excessive reactive oxygen species (ROS) and free radicals damage neurons, lipids, and DNA. This oxidative burden contributes to secondary injury cascades, worsening outcomes beyond the initial trauma. Antioxidants play a promising role in mitigating the effects of brain injury by counteracting oxidative stress, reducing inflammation, and supporting neural recovery. Consumption of antioxidant-rich diets, comprising vitamins C and E, polyphenols, carotenoids, and omega-3 fatty acids, has been associated with potential for mitigating secondary neurodegeneration and improving recovery outcomes. Emerging evidence supports that antioxidant-based nutritional interventions can facilitate neural plasticity, suppress inflammatory pathways, and enhance rehabilitation outcomes in motor and cognitive domains. This article explores the biological mechanisms and clinical implications of integrating antioxidant-rich diets with physiotherapy and cognitive rehabilitation following TBI.

Keywords: Antioxidants, Traumatic brain injury, Rehabilitation, Neural plasticity, Cognition

Introduction: Traumatic brain injury (TBI) persists as a critical public health challenge internationally, impacting diverse populations regardless of age or social status. Even with ongoing research breakthroughs and coordinated efforts among specialists, outcomes for patients remain suboptimal. Traumatic brain injury affects an estimated 939 out of every 100,000 people globally, with leading causes including falls, vehicular accidents, military conflict, and sports participation. Mortality rates for TBI worldwide fall between 7% to 23%, and about 90% of these deaths occur in low- and middle-income countries. Beyond its health consequences, TBI also exerts a profound economic impact, costing an estimated $400 billion annually across the globe (Dewan et al., 2018).

Traumatic brain injury (TBI) occurs when cerebral tissue absorbs energy from an external mechanical force. This energy disrupts metabolic, molecular, and biochemical networks, disturbing homeostatic balance of brain cells. As a result, TBI results in transient or lasting impairments, including loss in consciousness, cognitive impairments, motor function impairments, and mental health disorders (Carroll et al., 2004).

Traumatic brain injury is a complex disorder involving foremost mechanical damage leading to biochemical cascades, including oxidative stress, inflammation, and mitochondrial dysfunction. These processes contribute to neuronal loss, synaptic disruption, and impaired neural communication manifesting as cognitive and motor deficits (Maas et al., 2008).

Rehabilitation strategies such as physiotherapy, occupational therapy, and cognitive retraining are fundamental in functional recovery. However, optimal recovery also depends on cellular-level restoration, which can be influenced by nutritional status. Antioxidant-rich diets comprising fruits, vegetables, whole grains, and phytochemical compounds have emerged as adjunctive therapeutic tools to support neural repair and enhance the efficacy of rehabilitation interventions (Hall et al., 2010). This article reviews how antioxidant nutrition can synergize with rehabilitation to improve neurocognitive and motor outcomes in TBI patients.

Pathophysiology of Oxidative Imbalance Following Traumatic Brain Injury

Primary traumatic brain injury (TBI) results in immediate damage to cerebral cells and blood vessels. This initial insult triggers an array of molecular and biochemical processes collectively referred to as secondary injury. Secondary TBI begins immediately after impact and may persist potentially extending from hours to several weeks based on the degree of severity, results in a cascade that includes cerebral cellular necrosis and subsequent functional impairment of neurons. Key features include ionic imbalance and excessive discharge of excitatory neurotransmitters (specifically glutamate and aspartate). This triggers glucose dysmetabolism and mitochondrial dysfunction, which together contribute to the excessive overproduction of reactive free radicals. These processes activate multiple molecular networks and inflammatory signaling, which ultimately result in programmed cell death (apoptosis) and the compromise of the blood–brain barrier (BBB) integrity (Sahel et al., 2019).

Following traumatic brain injury (TBI), the generation of reactive oxygen species (ROS) and free radicals in cerebrum has been substantiated by numerous studies. These molecules initiate damaging processes such as lipid peroxidation (LP), DNA damage, and protein oxidation. In addition, they exacerbate glutamate excitotoxicity, mitochondrial dysfunction, ionic imbalance, and activation of cellular proteases, all of which contribute to secondary injury and progressive neuronal damage (Bullock & Fujisawa, 1992; Tymianski & Tator, 1996; Hall et al., 2010).

After TBI, the injured brain experiences excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These free radicals trigger lipid peroxidation, DNA damage, and mitochondrial dysfunction, amplifying neuronal injury. Key mechanisms include:

- Mitochondrial impairment, leading to reduced ATP production and increased oxidative stress.
- Inflammatory activation, involving microglia and astrocytes releasing cytokines (IL-1β, TNF-α).
- Calcium dysregulation, exacerbating excitotoxicity and apoptosis.

Neurorehabilitation enhance neuroplasticity, but their benefits can be limited when oxidative damage remains uncontrolled. Hence, antioxidant support can play a complementary role in mitigating these secondary injuries (Sahel et al., 2019).

Oxidative damage driven by free radicals, notably through membrane lipid peroxidation (LP), is among the most and stands as a firmly validated contributor to secondary injury in traumatic brain injury models. Beyond disrupting the phospholipid architecture of cell membranes, lipid peroxidation produces toxic aldehyde byproducts that covalently modify proteins, interfering with essential biological processes. Therapeutic strategies for acute traumatic brain injury (TBI) have largely focused on antioxidant neuroprotection by targeting single mechanisms within the secondary injury cascade. Approaches have implemented enzymatic pathways to scavenge superoxide radicals through superoxide dismutase (SOD) besides inhibiting lipid peroxidation with tirilazad. Despite extensive investigation, these interventions have not yielded consistent clinical success. A plausible explanation is that effective neuroprotection may require simultaneous or sequential interference across manifold stages of the oxidative damage cascade, rather than concentrating on a singular pathway (Marshall et al., 1998).

Employing two or three antioxidant interventions together may potentially enhance neuroprotective efficacy, reduce variability in outcomes, and extend the therapeutic window compared with single-agent approaches. Should these hypothesized advantages be substantiated in laboratory studies of TBI, such combinatorial interventions could substantially increase the likelihood of positive findings in forthcoming clinical trials, when compared with the limited results observed with single antioxidant therapies. Secondary injury is largely mediated by oxidative damage, specifically the free radical-induced peroxidation of membrane lipids (LP) following TBI. The LP produces highly neurotoxic aldehyde byproducts (Hall et al., 2010).

Several antioxidant agents have demonstrated efficacy in experimental TBI models. These include lipid peroxidation (LP) inhibitors such as U83836E, resveratrol, curcumin, OPC-14177, and lipoic acid; the iron chelator deferoxamine; and nitroxide-containing antioxidants such as α-phenyl-tert-butyl nitrone and tempol. A newer therapeutic approach involves the use of 'carbonyl scavenging' agents to target and neutralize aldehydic lipid peroxidation (LP) byproducts, which are known to be highly neurotoxic. The most promising therapeutic approach appears to be the combined use of mechanistically complementary antioxidants that target the oxidative cascade at multiple points: scavenging LP-initiating free radicals, inhibiting LP propagation, and removing toxic LP byproducts (Hall et al., 2010).

Numerous antioxidant strategies have been tested in animal models, including free radical scavengers, LP inhibitors (e.g., U83836E, resveratrol, lipoic acid), and iron chelators. These generally showed promising results, such as reduced edema, blood-brain barrier protection, decreased inflammation, and improved functional recovery (sensory, motor, and cognitive). A newer approach targets the neurotoxic aldehydic LP byproducts using "carbonyl scavenging" compounds. It was proposed that the most effective treatment for post-traumatic

oxidative brain damage may be a combined therapy (cocktail) using antioxidants whose mechanisms of action are mutually reinforcing and work together to:

1. Prevent the formation of new lipid peroxidation by scavenging precursor free radicals.
2. Inhibit LP propagation.
3. Facilitate the clearance of neurotoxic lipid peroxidation (LP) products (Hall et al., 2010).

Antioxidant-Rich Diets: Composition and Mechanisms (Hall et al., 2010).

Antioxidant-rich diets include nutrients and phytochemicals capable of neutralizing ROS, restoring redox balance, and promoting neuronal repair. Key components include:

Antioxidant	Dietary Sources	Mechanistic Role
Vitamin E (α-tocopherol)	Nuts,seeds, vegetable oils	Protects neuronal membranes from lipid peroxidation
Vitamin C (ascorbic acid)	Citrus fruits, berries	Regenerates vitamin E; scavenges free radicals
Polyphenols(flavonoids, resveratrol, curcumin)	Tea,grapes, turmeric	Modulate neuroinflammation and enhance synaptic plasticity
Carotenoids(β-carotene, lutein)	Carrots, spinach	Inhibit oxidative damage to neuronal lipids
Omega-3fattyacids(DHA, EPA)	Fish oil, flaxseed	Support neuronal membrane fluidity and neurogenesis

Tocopherols, a family of highly potent, lipid-soluble antioxidant agents, have demonstrated therapeutic potential in traumatic brain injury (TBI). Early post-injury administration of tocopherol has been shown to ameliorate reactive oxygen species (ROS)-mediated tissue pathology and support neuroregeneration. Tocopherol-succinate infusion has been associated with improvements in neurocognitive performance and motor function, suggesting possible clinical utility in mitigating TBI-related damage. Furthermore, reports indicate that tocopherol supplementation can mitigate oxidative protein degradation, re-establish homeostatic levels of superoxide dismutase (SOD) and brain-derived neurotrophic factor (BDNF), and enhance motor capabilities. Collectively, these findings indicate that dietary tocopherol may attenuate the detrimental influence of mild TBI on neuronal synaptic adaptability and higher-order cognitive processes (Clifton et al., 1989; Artuch et al., 2009; Aiguo et al., 2010; Yang et al., 2013).

As a lipid-soluble secosteroid, Vitamin D functions as an important hormonal mediator that could influence the recuperation trajectory following traumatic brain injury (TBI). Neuroinflammation may impair recovery, and may represent a key mechanism through which vitamin D exerts beneficial effects, as demonstrated in rat models of TBI. Literature demonstrates that vitamin D intake remains often inadequate compared by recommended dietary allowances (RDA). Consistent with this, Daradkeh et al.(2018) reported that nearly two-thirds of patients (66.7%) were found to be inadequate, while an additional 23.8% were categorized as deficient in serum vitamin D levels post-TBI (Hua et al.,2012; Hinson et al., 2015; Lawrence & Sharma, 2016; Daradkeh et al.,2018).

As an essential nutrient derived from a variety of foods, choline contributes to the synthesis of structural phospholipids, supports cellular signaling, and provides the building block for acetylcholine. Therefore, dietary choline supplementation has been proposed as a strategy to reduce cognitive impairments, mitigate neuroinflammation, and safeguard the penumbral region after traumatic brain injury (TBI). A choline-supplemented diet was shown to attenuate brain inflammation and preserve cortical tissue integrity (Blusztajn, 1998; Guseva et al., 2008).

Vitamin B3 (nicotinamide) has emerged as a promising neuroprotective compound in rodent models of cerebral ischemia. Administration within two hours of permanent focal ischemia induction significantly reduced infarct size. Consistent findings across different rat strains demonstrated both reduced infarct volume and improved neurological outcomes. A single dose of nicotinamide given within seven days of ischemia enhanced motor performance, while repeated dosing further improved behavioral outcomes. These results highlight the need for investigating nicotinamide's neuroprotective potential in ischemic brain injury (Ayoub et al., 1999; Sakakibara et al., 2000; Modudai et al., 2000; Maynard et al., 2001; Sakakibara et al., 2002).

Recent reviews have examined the practical role of micronutrient supplementation in nutrition therapy (Sriram & Lonchyna, 2009). Within this context, thiamine (vitamin B1) plays a particularly important role in certain disease states, including traumatic brain injury (TBI). Adequate dietary intake of thiamine (vitamin B1) is essential, as body reserves can be depleted within 20 days of insufficient oral intake. Thiamine plays a critical role in facilitating tissue healing via stimulation of antibodies, leukocyte generation, and collagen formation. Therefore, sufficient thiamine intake is particularly significant for individuals healing from traumatic injury or post-surgery. Thiamine plays a key role in fundamental cellular processes and enzyme-mediated reactions, its deficiency can result in severe and potentially disastrous consequences (Singleton & Martin, 2001; Sechi & Serra, 2007).

In a double-blind, controlled clinical trial, Razmkon et al. (2011) enrolled 100 patients with traumatic brain injury (TBI) then randomized them into four treatment groups: low-dose ascorbic acid (AA; 500 mg/day intravenously for 7 days), high-dose AA (10 g intravenously upon admission and again on day 4, followed by 4 g/day intravenously for 3 days), vitamin E (400 IU/day intramuscularly for 7 days), or placebo. Notably, patients receiving high-dose AA demonstrated beneficial effects, including reduced perilesional edema visualized through CT scanning (Razmkon et al., 2011).

Conclusion: The nutritional quality of the diet and/or the provision of pharmacological adjuvants and nutraceutical agents plays a pivotal role in affording protection against elevated reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation (Hasadsri et al.,2013). While link between oxidative/nitrosative damage and traumatic brain injury (TBI) is well established, and deficiencies in antioxidant-rich foods are plausibly associated with worsening TBI symptoms, there remains a dearth of clear clinical evidence supporting the use of antioxidant therapies (Rigg et al.,2005). Regardless of the wealth of research indicating promising outcomes with natural and synthetic low molecular weight antioxidants, TBI

treatment consistently lacks proof of therapeutic success based on these findings (Vonder Haar et al., 2016).

References:

1. Aiguo W, Zhe Y, Gomez-Pinilla F. Vitamin E protects against oxidative damage and learning disability after mild traumatic brain injury in rats. Neurorehabil Neural Repair. 2010;24:290-298.
2. Artuch R, Salviati L, Jackson S, Hirano M, Navas P. Coenzyme Q10 deficiencies in neuromuscular diseases. Adv Exp Med Biol. 2009;652:117-128.
3. Ayoub IA, Lee EJ, Ogilvy C. Nicotinamide reduces infarction up to two hours after the onset of permanent focal cerebral ischemia in wistar rats. Neurosci Lett. 1999;259:21-24.
4. Blusztajn JK. Choline, a vital amine. Science. 1998 Aug 7;281(5378):794-795.
5. Bullock R, Fujisawa H. The role of glutamate antagonists for the treatment of CNS injury. J Neurotrauma. 1992;9(Suppl. 2):S443-S462.
6. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG. WHO collaborating centre task force on mild traumatic brain injury. Methodological issues and research recommendations for mild traumatic brain injury: The WHO collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;43:113-125.
7. Clifton GL, Lyeth BG, Jenkins LW, Taft WC, DeLorenzo RJ, Hayes RL. Effect of D, alpha-tocopheryl succinate and polyethylene glycol on performance tests after fluid percussion brain injury. J Neurotrauma. 1989;6:71-81.
8. Daradkeh G, AL-Muhanadi A, ALsaadi R, Yazidi W, Lugan, Hammami M, Naeema. AL-Dahneem, Eman Abuhasan. Vitamin D insufficiency in post-traumatic brain injury patients from the state of Qatar. Int J Sci Res Method. 2018 Mar;9(1):247-259.
9. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, Agrawal A, Adeleye AO, Shrime MG, Rubiano AM, Rosenfeld JV, Park KB. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018 Apr 27;130(4):1080-1097.
10. Guseva MV, Hopkins DM, Scheff SW, Pauly JR. Dietary choline supplementation improves behavioral, histological, and neurochemical outcomes in a rat model of traumatic brain injury. J Neurotrauma. 2008;25(8):975-983.
11. Hall ED, Vaishnav RA, Mustafa AG. Antioxidant therapies for traumatic brain injury. Neurotherapeutics. 2010;7(1):51-61.
12. Hasadsri L, Wang BH, Lee JV, Erdman JW, Llano DA, Barbey AK, Wszalek T, Sharrock MF, Wang HJ. Omega-3 fatty acids as a putative treatment for traumatic brain injury. J. Neurotrauma 2013, 30, 897-906.
13. Hinson HE, Rowell S, Schreiber M. Clinical evidence of inflammation driving secondary brain injury: A systematic review. J Trauma Acute Care Surg. 2015;78:184-191.
14. Hua F, Reiss JI, Tang H. Progesterone and low-dose Vitamin and hormone treatment enhance sparing of memory following traumatic brain injury. Horm Behav. 2012;61:642-651.
15. Lawrence DW, Sharma B. A review of the neuroprotective role of vitamin D in traumatic brain injury with implications for supplementation post-concussion. Brain Inj. 2016;30(8):960-968.

16. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008; 7:728-741.
17. Marshall LF, Maas AI, Marshall SB, Bricolo A, Fearnside M, Iannotti F, Klauber MR, Lagarrigue J, Lobato R, Persson L, Pickard JD, Piek J, Servadei F, Wellis GN, Morris GF, Means ED, Musch B. A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. J Neurosurg. 1998 Oct;89(4):519-25.
18. Maynard KI, Ayoub IA, Shen C. Delayed multidose treatment with nicotinamide extends the degree and duration of neuroprotection by reducing infarction and improving behavioral scores up to two weeks following transient focal cerebral ischemia in Wistar rats. Ann. NY Acad Sci. 2001;939:416-424.
19. Modudai T, Ayoub IA, Sakakibara Y. Delayed treatment with nicotinamide (vitamin B3) improves neurological outcome and reduces infarct volume after transient focal cerebral ischemia in Wistar rats. Stroke. 2000;31:1679-1685.
20. Razmkon A, Sadidi A, Sherafat-Kazemzadeh E, Mehrafshan A, Jamali M, Malekpour B, Saghafinia M. Administration of vitamin C and vitamin E in severe head injury: A randomized double-blind controlled trial. Clin. Neurosurg. 2011, 58, 133-137.
21. Rigg JL, Elovic EP, Greenwald BD. A review of the effectiveness of antioxidant therapy to reduce neuronal damage in acute traumatic brain injury. J Head Trauma Rehabil. 2005 Jul-Aug;20(4):389-391.
22. Sahel DK, Kaira M, Raj K, Sharma S, Singh S. Mitochondrial dysfunctioning and neuroinflammation: Recent highlights on the possible mechanisms involved in Traumatic Brain Injury. Neurosci Lett. 2019;710:134347.
23. Sakakibara Y, Mitha AP, Ayoub IA. Delayed treatment with nicotinamide (vitamin B3) reduces the infarct volume following focal cerebral ischemia in spontaneously hypertensive rats, diabetic and non-diabetic Fischer 344 rats. Brain Res. 2002;931:68-73.
24. Sakakibara Y, Mitha AP, Ogilvy C. Post-treatment with nicotinamide (vitamin B3) reduces the infarct volume following permanent focal cerebral ischemia in female Sprague-Dawley and Wistar rats. Neurosci Lett. 2000;281:111-114.
25. Sechi G, Serra A. Wernicke's encephalopathy: New clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007;6:442-455.
26. Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. Curr Mol Med. 2001; 1:197-207.
27. Sriram K, Lonchyna VA. Micronutrient supplementation in adult nutrition therapy: Practical considerations. J Parenter Enteral Nutr. 2009;33:548-562.
28. Tymianski M, Tator CH. Normal and abnormal calcium homeostasis in neurons: A basis for the pathophysiology of traumatic and ischemic central nervous system injury. Neurosurgery. 1996;38:1176-1195.
29. Vonder Haar C, Peterson TC, Martens KM, Hoane MR. Vitamins and nutrients as primary treatments in experimental brain injury: Clinical implications for nutraceutical therapies. Brain Res. 2016 Jun 1;1640(Pt A):114-129.
30. Yang J, Han Y, Ye W, Liu F, Zhuang K, Wu G. Alpha tocopherol treatment reduces the expression of Nogo-A and NgR in rat brain after traumatic brain injury. J Surg Res. 2013;182:e69-e77.

ISSN PRINT 2319 1775 Online 2320 7876
 Journal UGC CARE Listed (Group-I) Volume 10, Issue 11 2021

Corresponding Address:

Dr. Maman Paul,

Assistant Professor,

Deptt. of Physiotherapy,

Guru Nanak Dev University, Amritsar, Punjab, India.

email: mamanpaul@gmail.com