

## Review Article

# Stuck at the bench: Potential natural neuroprotective compounds for concussion

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## Abstract

**Background:** While numerous laboratory studies have searched for neuroprotective treatment approaches to traumatic brain injury, no therapies have successfully translated from the bench to the bedside. Concussion is a unique form of brain injury, in that the current mainstay of treatment focuses on both physical and cognitive rest. Treatments for concussion are lacking. The concept of neuro-prophylactic compounds or supplements is also an intriguing one, especially as we are learning more about the relationship of numerous sub-concussive blows and/or repetitive concussive impacts and the development of chronic neurodegenerative disease. The use of dietary supplements and herbal remedies has become more common place.

**Methods:** A literature search was conducted with the objective of identifying and reviewing the pre-clinical and clinical studies investigating the neuroprotective properties of a few of the more widely known compounds and supplements.

**Results:** There are an abundance of pre-clinical studies demonstrating the neuroprotective properties of a variety of these compounds and we review some of those here. While there are an increasing number of well-designed studies investigating the therapeutic potential of these nutraceutical preparations, the clinical evidence is still fairly thin.

**Conclusion:** There are encouraging results from laboratory studies demonstrating the multi-mechanistic neuroprotective properties of many naturally occurring compounds. Similarly, there are some intriguing clinical observational studies that potentially suggest both acute and chronic neuroprotective effects. Thus, there is a need for future trials exploring the potential therapeutic benefits of these compounds in the treatment of traumatic brain injury, particularly concussion.

**Key Words:** Concussion, mild traumatic brain injury, neuroprotection, supplements, treatment

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## INTRODUCTION

Significant efforts have been made in recent years to

discover substances that can provide neuroprotection for diseases of the central nervous system (CNS). While numerous laboratory studies have searched for treatment

approaches to traumatic brain injury (TBI), no therapies have successfully translated from the bench to the bedside. Concussion is a unique form of TBI, in that the current mainstay of treatment focuses on both physical and cognitive rest. While many patients experience a spontaneous resolution of their acute post-concussive symptoms, the long term effects from the injury are still unclear. Additionally, we are learning more about the relationship of numerous sub-concussive blows and/or repetitive concussive impacts and the development of chronic neurodegenerative disease.

There has been an immense interest in natural compounds and nutraceuticals (i.e. food derivatives or dietary supplements and herbal remedies that provide health benefits). Some of these preparations and compounds have been used for centuries to treat illness and they have become more popular in society lately, particularly because of their relatively few side effects. Maroon *et al.*, recently published an excellent review of natural anti-inflammatory agents for pain relief.<sup>[139]</sup> It is important to continue to explore potential neuroprotective translational therapies for TBI, particularly concussion. An understanding of the pathophysiology underlying concussive brain injury is important when considering potential pharmacologic approaches. While not an exhaustive list, the subsequent sections will review some of the compounds and supplements that have preliminarily demonstrated potential neuroprotective benefits.

## MOLECULAR PATHOPHYSIOLOGY OF CONCUSSION

While the acute clinical symptoms of concussion are largely felt to reflect a functional disturbance; the mechanical trauma of a concussion does result in pathological changes at the ultra-structural level, which ultimately initiate a complex cascade of neurochemical and neurometabolic events.<sup>[15]</sup>

There is initially a disruption of the neurofilaments and microtubules that provide a framework for axonal transport. This compromises anterograde and retrograde transport of molecular proteins to and from somata.<sup>[15,141-143,168,173,186,210]</sup> Axonal transport can also be affected by delayed, progressive injury secondary to proteolysis.<sup>[94]</sup> At the cellular level, there is neuronal membrane disruption that leads to ionic shifts and an increase in intracellular glutamate and calcium.<sup>[15,102,141,168]</sup> Some cells may ultimately undergo caspase-mediated apoptosis as a result of these cellular changes. Inflammatory cascades also contribute significantly to further injury following TBI.

Additionally, two major glucose metabolism alterations have been described in association with concussion,

including hyperglycolysis and oxidative dysfunction.<sup>[15]</sup> Mitochondrial injury can also lead to failure in adenosine triphosphate (ATP) generation and an increase in reactive oxygen species.<sup>[225,243]</sup> Concussion may also compromise or alter the control of cerebral blood flow (CBF), cerebrovascular reactivity, and cerebral oxygenation.<sup>[121]</sup> The time-course of these pathophysiological events may have important implications in the success of various treatments for concussion patients.

There is also accumulating evidence that neuroinflammatory cascades play a significant role in the pathogenesis of disease following concussion and possibly repetitive subconcussive injury. The spectrum of post-concussive disease includes acute symptoms, post-concussion syndrome (PCS), prolonged post-concussion syndrome (PPCS), mild cognitive impairment (MCI), chronic traumatic encephalopathy (CTE), and dementia pugilistica (DP). The role of neuroinflammation and immunoexcitotoxicity in the genesis of these post-concussive processes has recently been reviewed.<sup>[25]</sup> If neuroinflammation is a possible common substrate, it would seem reasonable that therapeutic options should at least include some anti-inflammatory mechanisms of action. Many of the natural compounds reviewed here have multiple mechanisms of neuroprotection, including interfering with the post-traumatic inflammatory cascade.

## EICOSAPENTAENOIC ACID AND DOCOSAHEXAENOIC ACID

Omega-3 polyunsaturated fatty acids are important structural components of all cell membranes modulating membrane fluidity, thickness, cell signaling, and mitochondrial function.<sup>[62,190]</sup> Long-chain polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are highly enriched in neuronal synaptosomal plasma membranes and vesicles.<sup>[62]</sup> The predominant CNS polyunsaturated fatty acid is DHA which is readily retained in neuronal plasma membranes.<sup>[140]</sup> Neuronal DHA, in turn, influences the phospholipid content of the plasma membrane increasing phosphatidylserine and phosphatidylethanolamine production and promoting neurite outgrowth during both development and adulthood.<sup>[34,181]</sup> Despite DHA's importance for CNS function, the predominant dietary polyunsaturated fatty is linolenic acid obtained through ingestion of certain nuts and vegetable oils; which is inefficiently converted to EPA or DHA.<sup>[95]</sup> Therefore, effective supplementation and/or increased ingestion of dietary sources rich in EPA and DHA, such as cold-water fish species and fish oil, may help improve a multitude of neuronal functions, including long-term potentiation and cognition.<sup>[114,145,151]</sup>

With respect to neuroprotection in the context of improving outcomes following TBI, multiple

preclinical studies have suggested that DHA and/or EPA supplementation may have potential benefit through a multitude of diverse, but complementary mechanisms.<sup>[13,149,150,237,238]</sup> Studies utilizing rodent models of experimental injury have shown that pre-injury dietary supplementation with fish oil effectively reduces post-traumatic elevations in protein oxidation resulting in stabilization of multiple molecular mediators of learning, memory, cellular energy homeostasis and mitochondrial calcium homeostasis as well as improving

cognitive performance.<sup>[237,238]</sup> [Table 1] The benefits of pre-traumatic DHA supplementation have not only been independently confirmed,<sup>[150]</sup> but DHA supplementation has been shown to significantly reduce the number of swollen, disconnected and injured axons when administered following traumatic brain injury.<sup>[13,149]</sup> Of note, DHA has provided neuroprotection in experimental models of both focal and diffuse traumatic brain injury.<sup>[13,149,150,237,238]</sup> Studies in other models of neurologic injury have revealed a variety of potential mechanisms

**Table 1: Eicosapentaenoic acid and docosahexaenoic acid mediated multi-mechanistic neuroprotection**

Mechanism	Model	Agent	Summary	Reference(s)
Anti-oxidant	Cell culture	DHA	Increased activity of glutathione peroxidase and glutathione reductase	228
	Rat corpus callosum	Fish oil	Increased activity of superoxide dismutase Reduced activity of xanthine oxidase activity and nitric oxide levels	193
	Rat hypothalamus	Fish oil	Reduced activity of superoxide dismutase Decreased nitric oxide and tissue malondialdehyde (lipid peroxidation) levels	208
	Gerbil ischemia	DHA	Increased activity of glutathione peroxidase and catalase levels	35
	Rat TBI	Fish oil	Reduced protein oxidation	236, 238
Anti-inflammatory	Isolated monocytes	Fish oil	Decreased synthesis of IL-1 $\beta$ and TNF- $\alpha$	65
	Isolated monocytes	Fish oil	Decreased synthesis of TNF- $\alpha$ , IL-1, IL-6 and IL-8 Reduced monocyte-endothelium adhesion and transendothelial migration	144
	Cell culture	EPA	Inhibition of downstream mediators of JNK pathway	132
	Cell culture	DHA	Reduced expression of TNF- $\alpha$ , IL-6, NO synthase and COX-2 in microglia	133
Reduces excitotoxicity	Cell culture	DHA	Inhibition of glutamate-induced neuronal toxicity	228
	Rat nucleus basalis	Fish oil	Increased neuronal survival following NMDA-receptor activation	85
	Organotypic hippocampal slices	DHA	Reduced neuronal toxicity following AMPA-receptor activation	148
Mitochondrial protection	Rat TBI	Fish oil	Counteracted post-traumatic reductions in ubiquitous mitochondrial creatinine kinase (uMtCK)	238
Protection of brain metabolism	Cell culture	EPA/DHA	Increased blood-brain barrier glucose transport	170
	Rat TBI	Fish oil	Counteracted post-traumatic reductions in the silent information regulator 2 (Sir2) and ubiquitous mitochondrial creatine kinase	238
Neurite growth and neurogenesis	Cell culture	DHA	Increased neuron population and increased length of neurites	32
	Cell culture	DHA	Increased neuronal viability and increased length of neuritis	34
	Cell culture	EPA/DHA	Increased neurite outgrowth	181
Protects synaptic plasticity	Rat TBI	Fish oil	Counteracted post-traumatic reductions in brain derived neurotrophic factor (BDNF), synapsin I, and cAMP responsive element binding protein (CREB)	236

DHA: Docosahexaenoic acid, EPA: Eicosapentaenoic acid, TBI: Traumatic brain injury

of neuroprotection, in addition to DHA and EPA's well-established anti-oxidant and anti-inflammatory properties.<sup>[32,34,35,65,85,132,133,144,148,170,181,193,208,228,237,238]</sup> [Table 1].

Despite abundant laboratory evidence supporting its neuroprotective effects in experimental models, the role of dietary DHA and/or EPA supplementation in human neurological diseases remains uncertain. To date, there have been no clinical trials investigating the effects of DHA and/or EPA dietary supplementation on the treatment or prevention of TBI. Several population-based, observational studies have suggested that increased dietary fish and/or omega-3 polyunsaturated fatty acid consumption may reduce risk for ischemic stroke in several populations;<sup>[81,91,153]</sup> however, such benefit has not been observed in all populations studied.<sup>[31]</sup> Randomized control trials have also demonstrated significant reductions in ischemic stroke recurrence,<sup>[217]</sup> relative risk for ischemic stroke,<sup>[2]</sup> and reduced incidence of both symptomatic vasospasm and mortality following subarachnoid hemorrhage.<sup>[253]</sup> Multiple studies, on the other hand, have found no statistically significant reduction in neurological impairment following ischemic stroke<sup>[72,172]</sup> reductions in epileptic seizure frequency.<sup>[28,57,174,255]</sup> Clinical trials in Alzheimer's disease have also been largely ineffective.<sup>[175]</sup> The clinical evidence thus far appears equivocal; however, the overall difficulty in controlling for basal dietary intake of polyunsaturated fatty acids between experimental groups, lack of good study design and the significant heterogeneity of the studied patient populations makes all of these studies difficult to interpret collectively. Nonetheless, the multi-mechanistic neuroprotective properties and the positive preclinical findings associated with omega-3 polyunsaturated fatty acid supplementation warrant well designed clinical trials in the future to determine whether supplementation may improve outcomes following mild TBI.

## CURCUMIN

Curcumin is a flavonoid compound that is the principal curcuminoid of the Indian spice turmeric. It is also a member of the ginger family. While this natural phenol is most commonly known for providing the yellow pigment seen in many curries; curcumin has long been a staple of many traditional remedies offered by practitioners of Oriental and Ayurvedic medicine.<sup>[73]</sup> More recently, curcumin has gained much attention from Western researchers for its potential therapeutic benefits in large part due to its potent anti-oxidant<sup>[128,194,236]</sup> and anti-inflammatory properties.<sup>[3,115,139]</sup> Curcumin is highly lipophilic and crosses the blood-brain barrier enabling it to exert a multitude of different established neuroprotective effects [Table 2]. Multiple experimental animal models have suggested that curcumin supplementation may offer benefit in the treatment of chronic neurodegenerative

processes, such as Alzheimer's disease,<sup>[128,248]</sup> as well as acute neurological insults including ischemic stroke<sup>[61,93,203,221,247,259]</sup> and subarachnoid hemorrhage.<sup>[226]</sup>

Specifically in the context of TBI, a series of preclinical studies have suggested that pre-traumatic and post-traumatic curcumin supplementation may bolster the brain's resilience to injury and serve as a valuable therapeutic option.<sup>[115,201,202,236,239]</sup> Curcumin may confer significant neuroprotection because of its ability to act on multiple deleterious post-traumatic, molecular cascades. For example, pre-traumatic curcumin supplementation improved post-traumatic cognitive deficits and stabilized levels of certain proteins implicated in the molecular mechanisms underlying learning, memory, and cellular energy homeostasis.<sup>[115,202,236]</sup> [Table 2]. Additionally, these studies demonstrated that both pre- and post-traumatic curcumin administration resulted in a significant reduction of neuroinflammation via inhibition of the pro-inflammatory molecules interleukin 1 $\beta$  and nuclear factor kappa B (NF $\kappa$ B). More importantly, the reduced neuroinflammatory response mitigated post-traumatic reactive astrogliosis and prevented upregulation of the water channel aquaporin 4, thus reducing the magnitude of cellular edema. It was determined, though, that prophylactic administration of curcumin exerted greater neuroprotective effects than post-traumatic treatment and that the therapeutic window for significant neuroprotection, in these studies, was less than one hour post-TBI.<sup>[115]</sup>

Nonetheless, other studies have further evaluated the benefits of post-traumatic administration of a curcumin derivative, CNB-001, with enhanced neuroprotective properties.<sup>[131,201,239]</sup> These studies demonstrate that this compound is capable of significantly reducing post-traumatic elevations in lipid peroxidation and protein oxidation, as well as disturbances in plasma membrane turnover and phospholipid metabolism. Additionally, this curcumin derivative prevented reductions in proteins important for learning, memory, and synaptic transmission; and promoted cellular energy homeostasis [Table 2]. Post-traumatic administration of CNB-001 also improved injury-associated behavioral impairment,<sup>[201,239]</sup> thereby suggesting that curcumin-induced normalization of multiple molecular systems may help preserve neuronal structure and function during the post-injury period.

Therapeutic administration of curcumin in human patients has been shown to be well-tolerated.<sup>[16,59]</sup> However, despite a tremendous amount of laboratory evidence demonstrating the neuroprotective effects of curcumin; to date, no human studies have been conducted with respect to the effects of curcumin administration on the treatment of TBI, subarachnoid or intracranial hemorrhage, epilepsy or stroke. Preliminary clinical evidence in support of curcumin's

**Table 2: Mechanisms of curcumin mediated neuroprotection**

Mechanism	Model	Agent	Summary	Reference(s)
Anti-oxidant	Alzheimer's mice	Curcumin	Reduced protein oxidation	128
	Rat TBI	Curcumin	Reduced protein oxidation	237
	Rat TBI	CNB-001	Reduced lipid peroxidation	201
	Rat TBI	CNB-001	Normalized post-traumatic superoxide dismutase levels	239
	Rat ischemia	Curcumin	Counteracted reductions in glutathione peroxidase Decreased levels of reactive oxygen species, peroxynitrite and nitric oxide	61, 93, 221
	Rat ischemia	Curcumin	Increased activity of superoxide dismutase and reduced lipid peroxidation	203
Anti-inflammatory	Alzheimer's mice	Curcumin	Reduced levels of IL-1 $\beta$ and peri-neuronal microgliosis	128
	Mouse TBI	Curcumin	Reduced expression of IL-1 $\beta$ and inhibited NF $\kappa$ B Reduced reactive astrogliosis	115
	Rat ischemia	Curcumin	Counteracted post-ischemic neutrophil infiltration	61
Anti-apoptotic	Rat ischemia	Curcumin	Decreased levels of cytochrome c and cleaved caspase 3 expression Increased Bcl-2 expression	259
Protects blood-brain barrier	Rat ischemia	Curcumin	Reduced blood-brain barrier disruption	93
Decreases edema	Mouse TBI	Curcumin	Counteracted post-traumatic upregulation of astrocyte aquaporin-4	115
	Rat ischemia	Curcumin	Reduced edema following ischemic injury	61, 93
Mitochondrial protection	Rat TBI	Curcumin	Counteracted post-traumatic reductions in ubiquitous mitochondrial creatinine kinase (uMtCK), uncoupling protein 2 (UCP-2), and cytochrome c oxidase II (COX-2)	202
	Rat ischemia	Curcumin	Decreased levels of cytochrome c and increased Bcl-2 expression	259
Protection of brain metabolism	Rat TBI	Curcumin	Counteracted post-traumatic reductions in the silent information regulator 2 (Sir2), AMP-activated protein kinase (AMPK), uMtCK, UCP-2 and	237
	Rat TBI	CNB-001	Counteracted post-traumatic reductions in Sir2	239
Plasma membrane turnover	Rat TBI	CNB-001	Counteracted post-traumatic reductions in phospholipase A2 protein levels	201
Protects synaptic plasticity	Rat TBI	curcumin	Counteracted post-traumatic reductions in brain derived neurotrophic factor (BDNF), synapsin I, and cAMP responsive element binding protein (CREB)	237
	Rat TBI	CNB-001	Counteracted post-traumatic reductions in NMDA receptor NR2B subunit and syntaxin 3	201
	Rat TBI	CNB-001	Counteracted post-traumatic reductions in brain derived neurotrophic factor (BDNF), synapsin I, cAMP responsive element binding protein (CREB) and calcium/calmodulin-dependent protein kinase (CaMKII)	239

TBI: Traumatic brain injury

neuroprotective properties have come from several epidemiological studies. One study has suggested that

curcumin, a spice highly consumed in the Indian culture, may partially be responsible for the significant reductions

in Alzheimer's disease prevalence observed in India, when compared to the United States.<sup>[39]</sup> Another study has further suggested that increased curry consumption in an elderly population is associated with higher Mini Mental Status Examination scores.<sup>[159]</sup> In spite of these initial favorable findings, the results of more recent clinical trials in several Alzheimer's disease populations remain equivocal.<sup>[79]</sup> Whether curcumin intake or administration can afford significant neuroprotection in human TBI remains largely unknown and underexplored.

## RESVERATROL

Resveratrol is a naturally occurring phytoalexin and stilbenoid compound found in multiple dietary sources including redwine, grapes, and peanuts.<sup>[18]</sup> Since its original discovery in 1940, resveratrol has gained popular media attention for being the cardioprotective agent in red wine<sup>[26]</sup> and its capability of extending vertebrate lifespan.<sup>[17]</sup> Resveratrol has been demonstrated to effectively

cross the blood-brain barrier and improve outcomes in animal models following multiple acute neurological insults including stroke,<sup>[70,88,123,176,206]</sup> global cerebral ischemia,<sup>[58]</sup> spinal cord injury,<sup>[99,111,249]</sup> and TBI.<sup>[11,205,209]</sup> Resveratrol has also been demonstrated to slow the development of chronic neurodegenerative disease in animal models.<sup>[101,179]</sup> Although many of resveratrol's therapeutic benefits are classically attributed to its potent anti-oxidant effects,<sup>[11,18]</sup> numerous studies have identified additional mechanisms of neuroprotection [Table 3].

Preclinical studies have also explored resveratrol's therapeutic effect on experimental TBI. Studies have demonstrated that the post-traumatic administration of resveratrol reduces neuropathological and behavioral sequelae in both immature and adult rodents.<sup>[11,205,209]</sup> Resveratrol treatment in immature rodents reduced post-traumatic neuronal loss and improved behavioral measures of locomotion, anxiety, and novel object recognition memory.<sup>[209]</sup> In adult rodents, administration

**Table 3: Mechanisms of resveratrol neuroprotection**

Mechanism	Model	Agent	Summary	Reference(s)
Anti-oxidant	Rat ischemia	Resveratrol	Counteracted post-ischemia elevations in tissue malondialdehyde (lipid peroxidation) and reductions in brain glutathione	206
	Rabbit spinal cord ischemia	Resveratrol	Reduced spinal cord malondialdehyde (lipid peroxidation) levels	99
	Rabbit spinal cord ischemia	Resveratrol	Reduced spinal cord malondialdehyde (lipid peroxidation) and nitric oxide levels	111
	Rat TBI	Resveratrol	Counteracted post-traumatic elevations in malondialdehyde, xanthine oxidase and nitric oxide levels Increased post-traumatic glutathione levels	11
Anti-inflammatory	Rabbit spinal cord ischemia	Resveratrol	Reduced spinal cord neutrophil infiltration	99
	Cell culture	Resveratrol	Inhibited NFκB	100
Reduces excitotoxicity	Rat ischemia	Resveratrol	Reduced glutamate release and lessened excitotoxic index	123
Alterations of intra-neuronal mediators	Organotypic hippocampal slices	Resveratrol	Activated nicotinamide adenine dinucleotide-dependent deacetylase sirtuin 1 (SIRT1)	176
	Rat ischemia	Resveratrol	Activated nicotinamide adenine dinucleotide-dependent deacetylase sirtuin 1 (SIRT1)	58
Maintains extracellular matrix	Mouse ischemia	Resveratrol	Counteracted post-ischemic upregulation of matrix metalloproteinase-9 (MMP-9)	70
Decreases Edema	Rat spinal cord injury	Resveratrol	Reduced post-traumatic edema and improved Na <sup>+</sup> /K <sup>+</sup> -ATPase activity	249
	Rat TBI	Resveratrol	Reduced post-traumatic edema	11, 205

TBI: Traumatic brain injury

of resveratrol resulted in reduced levels of oxidative stress and lipid peroxidation and stabilized endogenous anti-oxidants following TBI.<sup>[11]</sup> Furthermore, studies have demonstrated that resveratrol treatment reduces brain edema and lesion volume, as well as improves neurobehavioral functional performance following TBI.<sup>[11,205]</sup> The molecular mechanisms underlying the aforementioned neuroprotection remain largely unknown.

To date, no human trials have been conducted to investigate the effects of resveratrol in the prevention or treatment of TBI. Resveratrol administration in some clinical studies has shown that resveratrol is capable of increasing cerebral blood flow<sup>[105]</sup> and reducing inflammation via inhibition of the pro-inflammatory molecule NFκB.<sup>[100]</sup> Epidemiological studies have also suggested that increased red wine consumption is associated with reductions in stroke risk.<sup>[155]</sup> However, it remains to be determined whether such protection is a result of improvements in other vascular and neuronal parameters or if it is even dependent on the presence of resveratrol. Therefore, further studies are needed to fully elucidate resveratrol's potential neuroprotective benefit, particularly in TBI.

## CREATINE

Creatine is an amino-acid like compound favored as a popular dietary supplement by many athletes for its promotion of muscle mass production. It also plays an integral role in the endogenous maintenance of cellular energy reserves in tissues with high and fluctuating energy demands, such as the brain and skeletal muscle. CNS creatine is derived from both its local biosynthesis from the essential amino acids methionine, glycine and arginine and through the transport of circulating peripherally-derived and/or dietary creatine across the blood-brain barrier.<sup>[19,161]</sup> Dietary creatine is predominately found in protein rich foods, such as meat, fish and poultry. Biochemically, creatine is readily phosphorylated by creatine kinase to yield the high-energy analogue phosphocreatine. Phosphocreatine may then transfer its N-phosphoryl group to adenosine diphosphate (ADP) creating one molecule of ATP, thereby replenishing cellular energy stores.<sup>[19]</sup> In the CNS, maintenance of cellular ATP levels is necessary for proper development and provides the cellular energy required to maintain the various cellular processes necessary for proper neuronal structure and function; including the maintenance of neuronal membrane potential, ion gradients underlying signal propagation, intracellular calcium homeostasis, neurotransmission, intracellular and intercellular signal transduction and neuritic transport.<sup>[19,241]</sup> More recent evidence also suggests that creatine may serve as a neuronal co-transmitter augmenting post-synaptic GABA signal transduction.<sup>[5,54,158,167]</sup> Studies of patients with

CNS creatine deficiency and/or murine models with genetic ablation of creatine kinase have consistently demonstrated significant neurological impairment in the absence of proper creatine, phosphocreatine, or creatine kinase function; thus highlighting its functional importance.<sup>[19,157]</sup>

Preclinical studies in a variety of experimental models have suggested that dietary creatine may provide neuroprotection in animal models of chronic neurodegenerative disease, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.<sup>[19,77]</sup> The neuroprotective effects may also be conferred in acute neurological injuries, such as TBI.<sup>[195,214]</sup> Of important note, mild TBI reduces brain creatine and phosphocreatine levels in rodent models, suggesting that resulting impairments in the maintenance of cellular energy may play a role in the evolution of secondary brain injury.<sup>[204]</sup> In rodents, pre-traumatic dietary supplementation with creatine monohydrate significantly reduced the magnitude of cortical tissue damage and the concentration of two biomarkers of cellular injury, free fatty acids and lactic acid, following experimental injury.<sup>[195,214]</sup> It was further elucidated that creatine-mediated neuroprotection is in part mediated by the maintenance of cellular ATP levels and improvements in mitochondrial bioenergetics; including increased mitochondrial membrane potential and reductions in mitochondrial permeability, reactive oxygen species, and calcium levels.<sup>[214]</sup> Additional mechanisms of neuroprotection in the context of TBI remain to be determined.

In humans, studies utilizing nuclear magnetic spectroscopy have demonstrated that creatine supplementation does indeed increase cerebral creatine and phosphocreatine stores. Additionally, chronic dosing may partially reverse neurological impairments in human CNS creatine deficiency syndromes.<sup>[77,157]</sup> Acute supplementation of creatine may also improve cognition in elderly patients and adults following sleep deprivation.<sup>[146,147]</sup> Several studies have suggested that creatine supplementation may also reduce oxidative DNA damage and brain glutamate levels in Huntington disease patients.<sup>[21,84]</sup> Another study highlighted that creatine supplementation marginally improved indices of mood and reduced the need for increased dopaminergic therapy in patients with Parkinson's disease.<sup>[22]</sup> Together, these data suggest that dietary creatine supplementation may effectively increase CNS creatine/phosphocreatine stores and may modulate human neurological disease.

No human studies have been conducted to investigate the effects of prophylactic creatine supplementation on increasing brain resilience to TBI. However, preliminary results obtained in a pediatric population have suggested that post-traumatic oral creatine administration (0.4 g/

kg) given within four hours of traumatic brain injury and then daily thereafter, may improve both acute and long-term outcomes.<sup>[188,189]</sup> Acutely, post-traumatic creatine administration seemed to reduce duration of post-traumatic amnesia, length of time spent in the intensive care unit, and duration of intubation.<sup>[188]</sup> At three and six months post-injury, subjects in the creatine treatment group demonstrated improvement on indices of self care, communication abilities, locomotion, sociability, personality or behavior and cognitive function when compared to untreated controls.<sup>[188]</sup> Further analysis of the same population, revealed that patients in the creatine-treatment group were less likely to experience headaches, dizziness and fatigue over six months of follow-up.<sup>[189]</sup> Most important, creatine treatment appeared to be well tolerated and there were no significant side effects reported,<sup>[188,189]</sup> which was consistent with other human studies utilizing higher dosages.<sup>[10,22,84]</sup> While initial studies have also provided encouraging preliminary evidence supporting the use of creatine supplementation in the treatment of primary depression,<sup>[182]</sup> whether creatine may serve as an effective treatment post-traumatic or post-concussive depression remains to be determined.

## GREEN TEA

Although enjoyed by many for simply its taste and ability to bolster alertness during a time of fatigue, green tea is comprised of a trio of protective compounds that have independently drawn the attention of researchers from several diverse disciplines including cardiology, oncology, rheumatology, and neurology. At the core of green tea's neuroprotective properties, are the flavanoid - epigallocatechin-3-gallate (EGCG), the amino acid - theanine and finally the methylxanthine - caffeine (discussed below). All three of these compounds have been shown to exert multiple *in vitro* and *in vivo* neuroprotective effects<sup>[14,78,97,106,108,138,178]</sup> [Table 4].

One of the most abundant compounds in green tea extract is the potent anti-oxidant EGCG which is capable of crossing the blood-nerve and blood-brain barrier,<sup>[156,212]</sup> and exerting neuroprotective benefits in animal models of peripheral nerve injury,<sup>[233]</sup> spinal cord trauma,<sup>[106]</sup> and ischemic stroke.<sup>[49,120,163]</sup> Epigallocatechin-3-gallate also displays neuroprotective properties in animal models of chronic neurodegenerative diseases including amyotrophic lateral sclerosis,<sup>[113,254]</sup> Parkinson's disease,<sup>[48,122,137]</sup> and Alzheimer's disease.<sup>[108,178]</sup> Epigallocatechin-3-gallate's neuroprotection has largely been attributed to its potent anti-oxidant<sup>[14,108,178,233]</sup> and anti-inflammatory properties,<sup>[106,138]</sup> however, a number of studies have identified additional neuroprotective mechanisms [Table 4].

Other animal studies have also demonstrated that

theanine, another important component of green tea extract, exerts a multitude of neuroprotective benefits in experimental models of ischemic stroke,<sup>[63,97]</sup> Alzheimer's disease,<sup>[109]</sup> and Parkinson's disease.<sup>[43]</sup> Theanine, like EGCG, contains multiple mechanisms of neuroprotective action including protection from excitotoxic injury<sup>[97]</sup> and inhibition of inflammation<sup>[109]</sup> [Table 4].

As with most other natural compounds, no human trials have been conducted to investigate the effects of EGCG and/or theanine on reducing or treating brain injury following TBI; however, preliminary evidence has suggested that green tea-derived compounds may indeed modulate neuronal function in human subjects. For example, a randomized, placebo-controlled trial demonstrated that administration of green tea extract and L-theanine, over 16 weeks of treatment, improved indices of memory and brain theta wave activity on electroencephalography, suggesting greater cognitive alertness.<sup>[165]</sup>

Additional studies have also suggested that green tea extract may decrease cognitive decline in the elderly<sup>[160]</sup> and that L-theanine and theogallin-enriched green tea or caffeine may increase brain theta wave activity and performance on tasks requiring attention, respectively.<sup>[60,103]</sup> Collectively, these studies suggest that green tea consumption or supplementation with its derivatives may bolster cognitive function acutely and may slow cognitive decline. However, sound evidence demonstrating green tea's neuroprotection in chronic neurodegenerative disease is lacking. At least one population based study, though, did demonstrate that increased green tea consumption was associated with a reduced risk for Parkinson's disease independent of total caffeine intake.<sup>[40]</sup> Future clinical and preclinical studies are needed to definitively address whether green tea may provide significant neuroprotection in TBI.

## CAFFEINE

Caffeine has assumed a unique position in western popular culture as a readily available psychoactive agent in tea, carbonated soft drinks and coffee required to combat periods of fatigue and increase mental alertness. Much less appreciated are the potential neuroprotective benefits from chronic caffeine consumption. Caffeine is a non-selective adenosine receptor antagonistic which may also influence CNS adenosine receptor levels following chronic, but not acute treatment.<sup>[125]</sup> Caffeine-mediated neuroprotection arises through adenosine-dependent effects, such as modulation of glutaminergic synaptic transmission, cell survival signal transduction and inhibition of neuroinflammation, as well as through adenosine-independent effects such as protection of the blood-brain barrier.<sup>[41]</sup> Significant caffeine-mediated neuroprotection has been demonstrated in animal models

**Table 4: Mechanisms of neuroprotection mediated by the green tea ingredients epigallocatechin-3-gallate and theanine**

Mechanism	Model	Agent	Summary	Reference(s)
Anti-oxidant	Diabetic Rats	EGCG	Reduced levels of malondialdehyde (lipid peroxidation) and nitrites	14
	Rat spinal cord injury	EGCG	Reduced inducible nitric oxide synthase and nitrotyrosine levels	106
	Rat peripheral nerve injury		Reduced neuronal nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) and neuronal nitric oxide synthase (nNOS)	233
	Rat Ischemia	EGCG	Reduced malondialdehyde (lipid peroxidation) and the level of oxidized:total glutathione ratio	49
	Parkinson's Mouse	EGCG	Reduced neuronal nitric oxide synthase	48
	Parkinson's mouse	EGCG	Prevented MPTP induced elevations in superoxide dismutase and catalase	122
	Mouse brain	Theanine	Increased brain glutathione levels and decreased protein oxidation and lipid damage	109
Anti-inflammatory	Rat spinal cord injury	EGCG	Reduced myeloperoxidase activity Attenuated post-injury elevations in TNF- $\alpha$ , IL-1 $\beta$ , COX-2	106
	Mouse ischemia	Theanine	Reduced post-ischemic microgliosis	63
	Mouse brain	Theanine	Inhibits activation of NF $\kappa$ B	109
Reduces excitotoxicity	Organotypic spinal cord slices	EGCG	Reduced glutamate level	254
Extracellular Matrix	Mouse ischemia	EGCG	Counteracted post-ischemic upregulation of matrix metalloproteinase-9 (MMP-9)	163
Neurite growth and neurogenesis	Cell culture	EGCG	Potentiated nerve growth factor induced neurite outgrowth	78
	Cell culture	Theanine	Prevented down-regulation of brain-derived neurotrophic factor and glial derived neurotrophic factor	43
Synaptic transmission	Mouse ischemia	Theanine	Modulated post-synaptic GABAA receptors	63
Tau and amyloid- $\beta$	Alzheimer's mice	EGCG	Reduced tau phosphorylation and amyloid- $\beta$ deposition	178

EGCG: Epigallocatechin-3-gallate

of chronic neurodegenerative disease such as Alzheimer's disease<sup>[7,8,33,55]</sup> and Parkinson's disease.<sup>[98,197,245]</sup>

The preclinical evidence regarding the neuroprotective effects of caffeine administration in TBI is equivocal.<sup>[4,24,41,125,232]</sup> It seems that chronic but not acute caffeine treatment leads to significant reductions in neurological deficits, cerebral edema, cellular apoptosis and inflammatory cell infiltrate following experimental injury. These improvements were attributed to upregulation of adenosine A<sub>1</sub> receptors which, in turn, suppressed the synthesis of pro-inflammatory cytokines and reduced glutamate release and subsequent excitotoxic injury.<sup>[125]</sup> Consistent with this report, previous studies have also suggested that chronic caffeine treatment is associated with diminished hippocampal neuronal

cell death following traumatic brain injury.<sup>[232]</sup> Other studies have demonstrated that selective adenosine A<sub>1</sub> agonists improve neuropathology following experimental injury,<sup>[224]</sup> whereas adenosine A<sub>1</sub> receptor genetic ablation worsens post-traumatic neuroinflammation and seizure activity.<sup>[80,112]</sup> Together, these studies suggest that chronic caffeine consumption may exert neuroprotective effects by modulating adenosine signaling in the brain. Yet another study demonstrated that post-traumatic caffeine treatment was associated with reductions in intracranial pressure.<sup>[24]</sup> Furthermore, the protective effects of post-traumatic caffeine administration were shown to be potentiated by its co-administration with alcohol.<sup>[56]</sup> In stark contrast, an independent study has reported that acute administration of high concentrations of caffeine just prior to traumatic injury worsened

mortality, inflammatory cell infiltrate, edema and blood-brain barrier disruption.<sup>[4]</sup> The sources underlying these apparent contradictions remains unclear, but necessitates careful consideration and caution regarding dosing, timing and duration of treatment if caffeine administration were to be translated into the clinical arena.

Population based studies have also yielded conflicting results regarding the utility of dietary caffeine intake in the prevention of human neurological disease. Several studies have identified that ingestion of coffee and/or tea are associated with reduced risk for cognitive decline,<sup>[192]</sup> Alzheimer's disease,<sup>[66,136,191]</sup> and Parkinson's disease,<sup>[9,53,183,185]</sup> suggesting that caffeine intake may provide protection from chronic neurodegenerative processes. One large population based, observational study found that consumption of three cups of coffee or tea per day, for ten years, lead to a 22 and 28% risk reduction in the development of Parkinson's disease.<sup>[216]</sup> The benefits are less clear for acute neurological diseases such as stroke. In certain populations, such as women, chronic coffee consumption was associated with a lower risk of ischemic stroke and subarachnoid hemorrhage.<sup>[117]</sup> However, in other populations chronic coffee intake has demonstrated no change in stroke risk<sup>[76]</sup> or in one study, even a transient increase in stroke risk immediately following ingestion.<sup>[152]</sup> Caffeine use has also been identified as a risk factor for subarachnoid hemorrhage<sup>[27]</sup> and intracerebral hemorrhage<sup>[69]</sup> in young patients.

To date, no formal clinical trials have been conducted to establish the effects of caffeine on reducing or treating TBI. Adenosine levels have been determined to be elevated in brain interstitial and cerebrospinal fluid (CSF) following traumatic brain injury,<sup>[20,50,180]</sup> although, the significance of these changes is unclear. Elevated CSF caffeine levels were associated with more favorable outcomes six months following TBI in one study.<sup>[187]</sup> While only a preliminary finding, this suggests that pre-traumatic caffeine ingestion may afford some degree of neuroprotection and improve outcomes following TBI.<sup>[187]</sup> It is still uncertain whether this benefit is associated with acute or chronic caffeine consumption and if so what amount.

## VITAMIN E AND C

Vitamins are generally associated with a positive connotation with respect to perceived health benefits. Preclinical and more recently clinical studies have begun to support the use of vitamins E and C in reducing neuropathology and cognitive deficits following brain trauma.<sup>[51,87,177,240]</sup> Of the numerous vitamins commercially available, vitamin E has been at the forefront of many studies investigating the potential neuroprotective benefits of vitamin supplementation. Vitamin E is a collective term for eight naturally occurring compounds,

four tocopherols (alpha-, beta-, gamma-, and delta-) and four tocotrienols (alpha-, beta-, gamma-, and delta-).<sup>[223]</sup> Vitamin E is a potent, lipid-soluble, anti-oxidant that is present in high concentrations in the mammalian brain.<sup>[211]</sup> In several animal models of brain injury such as ischemic stroke,<sup>[107,162]</sup> subarachnoid hemorrhage<sup>[104,222]</sup> and Alzheimer's disease,<sup>[215]</sup> administration of alpha-tocopherol or its potent derivative alpha-tocotrienol has been shown to lessen oxidative stress and neuropathology. Other laboratory studies have demonstrated that pre-traumatic alpha-tocopherol supplementation reduces TBI-induced increases in lipid peroxidation and oxidative injury and impairments in spatial memory.<sup>[87,240]</sup> Additional studies in transgenic mouse models of Alzheimer's disease have further demonstrated that pre- and post-traumatic vitamin E supplementation reduces lipid peroxidation, amyloidosis, and improves cognitive performance following repetitive concussive brain injury.<sup>[51]</sup>

Despite considerable promise in many animal models, the effectiveness of vitamin E supplementation in preventing and/or treating neurological disease in human patients have yielded conflicting results. Several population based studies have found vitamin E-associated reductions in ischemic stroke risk;<sup>[52,196]</sup> whereas, others have failed to find such an association.<sup>[23,30,64,198]</sup> Additionally, several of these studies have noted an increased risk for hemorrhagic stroke, warranting caution for widespread usage.<sup>[196,198]</sup> While recent studies have reported that vitamin E supplementation in MCI and Alzheimer's disease patients has proven largely ineffective,<sup>[89]</sup> such claims have been controversial and there are several factors to consider when critically reviewing the results of these studies. For starters, the doses used in these trials were quite low. Additionally, these clinical trials explored the effectiveness of alpha-tocopherol, the least active form of vitamin E. Despite being the major form of vitamin E in US diets, gamma-tocopherol has received little attention when compared to alpha-tocopherol which is generally found in supplements.<sup>[223]</sup> Gamma-tocopherol is the main anti-inflammatory component and has been found to be more effective in scavenging free radicals and nitrogen oxygen species that cause inflammation. Interestingly, the use of alpha-tocopherol supplements also significantly reduces serum gamma-tocopherol, and therefore, any potential health benefits of alpha-tocopherol supplements may be offset by deleterious changes in the bioavailability of other forms of potent tocopherols and tocotrienols.<sup>[223]</sup> One other point of consideration is that in neurodegenerative disease states like Alzheimer's disease and Parkinson's disease, where there are high levels of reactive oxygen species generation, vitamin E can tend to become oxidized itself. For maximal effectiveness and to maintain its anti-oxidant capacity, vitamin E must be given in conjunction with other anti-oxidants like vitamin C or flavonoids. These various factors might account for

the null effects of alpha-tocopherol supplementation in patients with MCI and Alzheimer's disease.<sup>[223]</sup>

In contrast, emerging evidence has suggested that daily intravenous administration of vitamin E following TBI significantly decreases mortality and improves patient outcomes when assessed at discharge and at two and six month follow-up time points.<sup>[177]</sup> Importantly, no increase in adverse events was detected. This study also identified that high dose vitamin C administration following injury stabilized or reduced peri-lesional edema and infarction in the majority of patients receiving post-injury treatment.<sup>[177]</sup> Like vitamin E, vitamin C, also known as ascorbic acid, is a potent anti-oxidant present in high concentrations in the CNS. Given these similarities in action, it has been speculated that combined vitamin C and E therapy may potentiate CNS anti-oxidation and act synergistically with regards to neuroprotection. There are few studies that have investigated combination therapy; however, one prospective human study has found that combined intake of vitamin C and E displays significant treatment interaction and reduces the risk of stroke.<sup>[52]</sup> Future studies are needed to confirm whether vitamin C or E monotherapy improves outcomes following TBI and whether combined therapy may further potentiate any protective benefit.

## VITAMIN D

Vitamin D is structurally similar to many sterol hormones and is obtained through both dietary intake and endogenous biosynthesis from cholesterol in the skin. Following intake or biosynthesis, Vitamin D undergoes enzyme catalyzed sequential hydroxylation to yield its active form 1,25-dihydroxyvitamin D or calcitriol. Despite being established to play a vital role in calcium homeostasis peripherally, the functional role of vitamin D in the CNS has remained elusive. Recent research has suggested that the cells in the brain not only possess the hydroxylase responsible for vitamin D activation, but that multiple regions in the brain abundantly express the nuclear vitamin D receptor.<sup>[68]</sup> Binding of vitamin D to its nuclear receptor, in turn, leads to its association with other transcription factors, such as retinoic acid receptor. Subsequently this complex binds to vitamin-D response elements in genomic DNA, thus augmenting gene transcription. Vitamin D-induced alterations in gene transcription are now believed to modulate a myriad of neuronal properties including proliferation, differentiation and maintenance of calcium homeostasis.<sup>[68]</sup>

Vitamin D deficiency is endemic in the adolescent, adult, and elderly populations in the United States,<sup>[38,75,220]</sup> and has been associated with inflammatory, autoimmune, cardiovascular, neuromuscular, and neurodegenerative diseases as well as cancer.<sup>[38]</sup> Population based studies have suggested that vitamin D deficiency in the elderly

is indeed associated with an increased prevalence of Parkinson's disease<sup>[67]</sup> dementia, Alzheimer's disease, increased stroke risk and a higher prevalence of MRI findings suggestive of primary cerebrovascular lesions.<sup>[29]</sup> The association between vitamin D deficiency and elevated stroke risk or other cardiovascular disease has been confirmed in other studies.<sup>[6,171]</sup> Furthermore, a randomized controlled trial has suggested that post-ischemic administration of vitamin D may improve endothelial cell function.<sup>[234]</sup> These studies, albeit anecdotal, suggest that vitamin D may indeed possess both neuroprotective and vasculoprotective properties.

More recent research has suggested that vitamin D supplementation and the prevention of vitamin D deficiency may serve valuable roles in the treatment of TBI and may represent an important and necessary neuroprotective adjuvant for post-TBI progesterone therapy.<sup>[12,37,38]</sup> Progesterone is one of the few agents to demonstrate significant reductions in mortality following TBI in human patients in preliminary trials<sup>[235,242]</sup> and phase III multi-center trials currently in progress. Similarly, *in vitro* and *in vivo* studies have suggested that vitamin D supplementation with progesterone administration may significantly enhance neuroprotection.<sup>[12]</sup> Vitamin D deficiency may increase inflammatory damage and behavioral impairment following experimental injury and attenuate the protective effects of post-traumatic progesterone treatment.<sup>[37]</sup>

## SCUTELLARIA BAICALENSIS

The root *Scutellaria baicalensis* is one of the most widely utilized traditional Oriental herbal remedies. It has been utilized in a number of diverse conditions including bacterial infections, inflammatory conditions, and more recently neurological disease. At the core of its potent protective bioactivity, are a trio of flavanoids, including baicalein, baicalin, and wogonin; each independently demonstrated to possess neuroprotective properties both *in vitro* and *in vivo*. Prior studies have demonstrated that baicalein and baicalin possess potent anti-oxidant abilities,<sup>[71,82]</sup> whereas wogonin potently attenuates microglial activation and resultant neuroinflammation.<sup>[118,169]</sup> Independent studies have further demonstrated that baicalein and baicalin may also have anti-inflammatory properties through the inhibition of the proinflammatory molecule NFκB<sup>[213,246]</sup> and microglial activation.<sup>[124]</sup> Comparison studies have also demonstrated that baicalein may protect neurons from both excitotoxic and glucose deprivation injury, while baicalin proved to be protective in excitotoxic injury and wogonin exerted no direct neuroprotective benefit in either *in vitro* model.<sup>[119]</sup> Other models have suggested that wogonin does promote neurite outgrowth<sup>[129]</sup> and indeed protects neurons from

oxygen/glucose deprivation,<sup>[207]</sup> in addition to excitotoxic and oxidative injury.<sup>[44]</sup> Baicalein has been shown to protect neurons from endoplasmic stress-induced apoptosis as well.<sup>[47]</sup> It remains unclear as to which flavanoid, if any, predominates with respect to *Scutellaria*-derived neuroprotection.

These potent anti-oxidant, anti-inflammatory and anti-apoptotic mechanisms have been explored in a multitude of other experimental models including cerebral ischemia,<sup>[45,86,110,199,200]</sup> cerebral reperfusion injury,<sup>[246]</sup> spinal cord injury,<sup>[36,256]</sup> Alzheimer's disease<sup>[134]</sup> and Parkinson's disease.<sup>[134,154]</sup> Importantly, in one model of experimental TBI, post-traumatic administration of baicalein decreased protein levels of pro-inflammatory cytokines, reduced cortical contusion volume and improved neurological outcome.<sup>[42]</sup> Whether baicalin and wogonin also possess protective effects with respect to TBI remains to be determined. Despite these positive preliminary findings in models of CNS disease, including TBI, no human studies have been conducted to evaluate whether the administration of *Scutellaria* provides neuroprotective benefits.

## OTHER NEUROPROTECTIVE NUTRACEUTICALS

There are numerous other herbal remedies, while previously utilized strictly within the realm of traditional Oriental medicine, are now becoming more appreciated for their multi-mechanistic neuroprotective benefits. One such compound known as danshen, comprised of the root *Salvia miltiorrhiza*, has been utilized for centuries as a traditional Chinese remedy for coronary artery and cerebrovascular disease. At least one study in human subjects has confirmed that chronic ingestion may indeed decrease the risk of stroke as well as stroke recurrence.<sup>[1,244]</sup> More recently, it has been shown that the bioactive compounds of *Salvia miltiorrhiza* extract providing much of the neuroprotective benefit are salvianic acid and lipid-soluble tanshinones.<sup>[116,227,230]</sup> These compounds have been shown to reduce lipid peroxidation and mitochondrial permeability,<sup>[229,230]</sup> stabilize of intracellular calcium,<sup>[83]</sup> reduce neuroinflammation,<sup>[219]</sup> and protect the blood-brain barrier.<sup>[218,257]</sup> Its neuroprotective effects have been investigated in experimental models of stroke,<sup>[116,218]</sup> Parkinson's disease<sup>[230]</sup> and Alzheimer's disease.<sup>[130]</sup> It is unknown whether significant benefit is associated with administration of *Salvia miltiorrhiza* derivatives in either experimental models of TBI or human TBI.

Another traditional remedy which has demonstrated significant neuroprotective potential is the potent anti-inflammatory<sup>[46,139]</sup> and anti-oxidant<sup>[90,166]</sup> compound derived from the bark of the maritime pine tree, Pycnogenol. In experimental models, Pycnogenol has demonstrated the ability to slow or reduce the

pathological processes associated with Alzheimer's disease.<sup>[90,166]</sup> Similarly, Pycnogenol administration, in a clinical study of elderly patients, led to improved cognition and reductions in markers of lipid peroxidase.<sup>[184]</sup>

Yet another example of a potential natural neuroprotective agent that has been widely studied is ginseng. Ginseng is comprised of multiple neuroactive compounds including ginsenosides and saponins that possess multiple mechanisms of neuroprotection including the ability to reduce brain oxidation<sup>[258]</sup> and neuroinflammation,<sup>[96,231]</sup> protect mitochondrial function,<sup>[252]</sup> promote neurogenesis,<sup>[260]</sup> and promote expression of several neurotrophic factors.<sup>[127]</sup> In experimental models, ginsenosides and/or saponins have been demonstrated to exert protection in cerebral ischemia,<sup>[164]</sup> stroke,<sup>[250-252,260]</sup> subarachnoid hemorrhage,<sup>[126]</sup> Parkinson's disease<sup>[135]</sup> and Alzheimer's disease.<sup>[231]</sup> It is also thought to protect cognitive function during aging.<sup>[258]</sup> Preclinical studies in at least one experimental model of TBI have suggested potential benefit in improving neuropathological and behavioral outcomes.<sup>[92]</sup> In humans, though, it remains unclear as to whether chronic administration of ginseng may improve cognition and/or slow progression of dementia.<sup>[74]</sup>

## CONCLUSION

The use of dietary supplements and herbal remedies has become more common place. There are several issues that do arise when considering the use of these compounds as adjuvant therapy for CNS disease. For instance, not all preparations available over the counter are standardized across the board regarding the quantity or concentrations of compound in the products and thus quality control becomes an issue. Also, little is known about the most optimal dose or amount of consumption necessary to see a clinical effect. Potential interactions with other nutraceuticals or prescription medications are common and it is paramount to have a sound understanding of their biological mechanisms of action. Nonetheless, there are an abundance of pre-clinical studies demonstrating the neuroprotective properties of a variety of these compounds.

Multiple mechanisms lead to secondary damage after TBI including ischemia, activation of neuronal death cascades, cerebral swelling, and inflammation. The development of neurochemical, histopathological, and molecular techniques to study TBI has enabled researchers to gain new insights into the mechanisms underlying posttraumatic tissue damage and associated neurological dysfunction. Despite the technological advances made during the last several decades, there still is no effective neuroprotective therapy currently available for mild let alone severe TBI. The mainstay of treatment for patients

with concussions is rest and while the majority of patients have a spontaneous resolution of their symptoms over a short period of time, approximately 10-20% of patients will have persistent symptoms and develop PCS or PPCS. We are also learning more about the long-term neurodegenerative processes that may result from repetitive concussive and sub-concussive brain injury, including MCI, CTE, and DP. Neuroinflammation appears to be a common thread with all of these disease processes.<sup>[25]</sup> Numerous pharmacological agents have been explored as potential therapeutic interventions aimed at ameliorating secondary damage after TBI, but without much success. It is likely that successful therapy for severe TBI may require favorable effects on multiple deleterious cascades rather than targeting a single pathophysiological mechanism. One of the intriguing aspects of many of these natural compounds is that they possess multiple mechanisms of neuroprotection, particularly anti-inflammatory properties.

While there are an increasing number of well-designed studies investigating the neuroprotective potential of these nutraceutical preparations, the clinical evidence is still fairly thin. There is a need for future trials exploring the potential therapeutic benefits of these compounds in the treatment of TBI, particularly concussion.

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## Commentary

## The use of neuroprotective nutraceuticals in traumatic brain injuries

Overall the authors put together an excellent overview of the scientific basis for the beneficial effects of a select number of nutraceuticals utilizing *in vitro* and some *in vivo* studies as they relate to concussive brain injuries. Their selection of nutraceuticals for discussion is also to be commended, as these have shown considerable beneficial effects in TBIs and/or other neurological disease models.

In my view, the only weakness of the paper was its discussion of the clinical studies, in which they gave an overall impression of poor or equivocal results for most nutraceuticals. Even though the authors note that many clinical studies suffer from methodological and other study design problems, I think further elaborations on the deficiencies of such studies needs to be discussed.

Unfortunately, a number of the studies they referenced were misquoted or the authors of the papers themselves omitted reported positive results buried within the paper's data. For example, they implied that most studies found no beneficial effects using omega-3 oil (N-3 oil) supplementation in seizure patients. They quote DeGiorgio *et al.* as finding no benefit using omega-3 oils in patients with chronic epilepsy, when in fact they found a positive trend in reduction in the severity of the seizures, but no reduction in the frequency of seizures. Yuen *et al.*, which they also quote as finding no benefit, in fact found that seizure frequency was significantly reduced for the first 6 weeks of treatment, but then the effect was not sustained.

I have treated a number of seizure patients of varying severity and duration with nutraceutical products, many of whom were on a number of anti-seizure medications, and have had great success in dramatically reducing the need for medications or, in some cases, eliminating the need for medications altogether. To accomplish this goal, one needs to approach the disorder not only from its pathophysiology, but also the patient's reaction to dietary influences. For example, the typical American diet contains large amounts of excitatory food additives, which are known to play a major role in epilepsy. It makes little sense to attempt pharmaceutical treatment of a patient's seizures while they are consuming high doses of the very amino acid driving the seizures. We also know, from large nutritional surveys, that a majority of Americans are deficient in magnesium. Magnesium is essential for modulation of NMDA receptors and low magnesium significantly lowers seizure thresholds.

Considerable evidence shows that seizures, as well as TBIs are an immunoexcitotoxic disorders, with elevations in cytokines, particularly TNF- $\alpha$ , and an increase in

calcium-permeable AMPA receptors in the hippocampus and cortex. This has been demonstrated specifically in the case of seizures.<sup>[3,5]</sup> In addition, high sugar intake, especially high fructose corn syrup, increases advanced glycation end products (AGEs), which stimulate RAGE receptors on microglia, again driving brain inflammation and generating high levels of free radicals. Likewise, a high intake of omega-6 oils (N-6 oils), as occurs in the typical Western diet, increases brain inflammation and has been shown to worsen seizures. So we see that merely altering the omega-3 intake is not sufficient to curtail seizures. One must also consider the N-6/N-3 ratio. A high intake of N-6 oils drives out beneficial N-3 oils, greatly increasing brain inflammation. Most studies never look at the participants' N-6 oil intake.

I find the same problem in their analysis of the studies on vitamin E, C and omega-3 oils in neurodegenerative disease prevention and treatment. If one actually looks at the data within these studies, that is, when the data is actually provided, one sees evidence that is not included in the abstract or the paper's final conclusion. For example, they quote Sasso *et al.* concerning the Physician Health Study using vitamin C and E as indicating they found no benefit of either supplement in preventing strokes, when in fact that is not exactly what the authors of the study found. Among 754 males having CVD at the baseline there was a 26% reduction in stroke incidence among those taking the vitamin E and C. As with all such studies one of the major problems is compliance. They reported that compliance at 4 years was 78%, but like all such studies compliance is self-reported by the participants.

I was also interested in the type of supplements used in the studies quoted. The only information available was that the authors of these studies used a synthetic form of alpha-tocopherol and ascorbic acid. The doses were quite low—400IU every other day for the vitamin E and 500 mg a day for the vitamin C. Smokers have been shown to have severe depletion of vitamin C and it takes high doses of vitamin C just to return the serum levels to normal. This would mean that to truly test high dose vitamin C one would require much higher doses over an extended time period than were used in this study. The vitamin E in many of these studies would average 200 IU a day, which again, is extremely low and one would not expect a significant effect.

The form of vitamin E is also essential, which the authors of this paper address. Natural vitamin E is normally composed of 4 subtypes, alpha, beta, gamma and delta tocopherols and 4 subtypes of tocotrienols, alpha, beta,

gamma and delta. The only anti-inflammatory form of natural vitamin E is the gamma fraction. Alpha-tocopherol is considered a much weaker antioxidant form of vitamin E as compared to natural vitamin E (mixed tocopherols). In some of the quoted studies they used DL-alpha-tocopherol, which has very poor antioxidant function and is poorly absorbed. The supplements used in most of these studies were donated by the manufacturers, and many are cheaply made and of poor quality. High quality supplements containing mixed tocopherols are relatively expensive and as such are rarely used in large population studies.

I have found that many clinical researchers seem to know little about free radical and lipid peroxidation chemistry and even less about naturally occurring antioxidants. As a result, many of these papers are seriously flawed. For example, the vitamin antioxidants in general are excellent in neutralizing a number of reactive oxygen species, but have little activity against lipid peroxidation products (acrolein and 4-hydroxynonenal) and reactive nitrogen species (RNS).<sup>[4]</sup> As a result, one would not expect a study, which used one or even two antioxidant vitamins to have much impact on diseases associated with high levels of RNS and lipid peroxidation products. For example, in chronic traumatic encephalopathy, TBI, strokes and the major neurodegenerative disorders one sees very high levels of reactive nitrogen species (peroxynitrite) and 4-hydroxynonenal/acrolein, which many consider to be the major damaging radicals.<sup>[1]</sup>

I have also found that many of those doing these clinical studies do not understand the functional particulars of the antioxidant network. In biological systems, we see an array of antioxidant systems, which interact to not only protect against a wide variety of reactive species, but also to prevent oxidation of the antioxidant molecules themselves. For instance, in a condition where one sees very high levels of oxidative stress, as for example, in Alzheimer's disease, supplementing with a single vitamin such as vitamin E will not only have little chance of success, but can potentially make things worse. This is because the vitamin E is eventually oxidized itself, and becomes a free radical.<sup>[2]</sup> The same occurs with the carotenoids and vitamin C. The flavonoids and the thiols (R-lipoid acid) play a major role in protecting the antioxidant vitamins from oxidation. The lesson is, one cannot treat nutraceuticals the same way one treats pharmaceuticals—they are not drugs. There is considerable essential synergism between many nutraceuticals and one must keep in mind that they function as a network.

One must also keep in mind that for over 20 years clinical trial studies suggested that a higher intake of omega-3 oils had no real impact on cardiovascular mortality. Today, most cardiologists accept that it has a tremendous

beneficial effect. One problem in the early studies was the fact they were not using a true placebo to compare results. Placebos are supposed to be inert physiologically. Many of these negative studies used olive oil as a placebo, which also has beneficial cardiovascular effects, making the studies invalid. Many placebos used in clinical research today are also not inert. As pointed out by critics, in a great number of clinical trials the placebo is not even named, making it impossible to evaluate the reliability of the study. In many of the clinical studies quoted by the authors, the papers never consider the effect of different intakes of flavonoid-containing foods on the outcome. If, for example, more people in the placebo group were eating a high flavonoid diet it will reduce the observed effect of the supplement in question. We have seen this bias in a great number of cancer-diet population studies.

This paper clearly demonstrates the beneficial effects of a number of nutraceuticals in animal models of human disease. One of the major puzzles is why do these substances work so well in animal models but not in clinical studies. Besides the factors discussed above, one must consider species differences in metabolism, absorption and tissue bioavailability and differences in the clinical aspects of the animal models. For example, many animal models will develop the pathological picture of human Alzheimer's disease, but not the clinical aspects—that is, the actual dementia. Yet, when animal models utilizing many different species are showing the same beneficial effects, they cannot be ignored. In addition, the animal's diet is carefully controlled in the study of disease models, but not in human trials, despite attempts to do so.

A number of clinical studies have shown that hospitalized patients have a high incidence of nutritional impairment, either as a full-blown clinical deficiency or subclinical deficiency at the time of admission and that in ICU patients this deficiency increases significantly during the hospital stay. A number of studies have also shown that nutritional supplementation during hospitalization reduces complications and length of the hospital stay. This cannot be ignored. The review by the authors did not include a number of clinical studies that did show a significant impact of using selected nutraceuticals on neurological disease prevention and outcomes.

Finally, we must face the growing recognition that sponsoring industries, primarily pharmaceutical manufacturers, are instilling a bias in a number of high impact clinical studies so as to favor company interest. It is recognized by both clinicians and pharmaceutical executives that clinical trials are powerful tools that can shape the practice of medicine. Increasingly, these companies have witnessed an encroachment on their profits by the use of nutraceutical by an increasing percentage of the population. By using biased clinical

trials to lessen interest in the use of these nutraceutical, they can avoid a loss of profits. While an increasing number of the major clinical journals have disclosure policies, few actually contain printed conflict disclosures in conjunction with the published article. In most cases disclosure is voluntary.

Overall, this study has been excellently presented and clearly shows the potential benefits of nutraceuticals in the prevention and treatment of neurological disorders. I feel that all practicing neurosurgeons and neurologists should read and study this important paper.

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## Commentary

### Neuroprotection and treatment for post concussion syndrome

The current treatment of PCS includes rest and withdrawal from most activities, the treatment of headaches with analgesics, depression with antidepressants and insomnia with hypnotics. Little, if any, attention is given to the underlying pathogenesis of the above symptomatology.

There is an extensive literature that documents the immunologic and excitotoxic cascade that occurs even with mild traumatic brain injury (TBI). We have recently summarized this literature and put forth a unifying hypothesis of immunoexcitotoxicity that we believe forms the underlying substrate in most cases of PCS, post traumatic shock disorder (PTSD) and chronic traumatic encephalopathy (CTE).<sup>[1]</sup>

In these disorders there is an overreaction of microglia, the innate immune protective cells in the brain to trauma. If “primed” by prior head injuries or other causes such as a prior infection, neurotoxic metals (Al, Hg, Cd, Fe) or neurotoxic chemicals (pesticides/herbicides), the immunoexcitotoxic response, normally protective, becomes neuro destructive. Memory loss, personality changes, depression and more all may result.

The paper by Petraglia, Winkler and Bailes is an extension of the prior work by Bailes, et al which described the importance of Omega 3 fatty acids (DHA) as a neuroprotectant in a laboratory model.<sup>[2]</sup> Many laboratories are searching for pharmacologic agents that may be neuroprotective and neurotherapeutic following traumatic brain injury.<sup>[3]</sup> This is one of the first papers to outline several natural compounds which act directly to counter the inflammatory and excitotoxic response

following TBI.

Omega 3 fatty acids (fish oil), resveratrol, green tea, creatine and curcumin are all potent natural compounds that block NF κB, a primary transcription factor regulating the neuro-inflammatory response. They also are strong antioxidants, protect against lipid peroxidation, contribute to neuroplasticity and enhance mitochondrial function and biogenesis and suppress microglial activation.

Pharmacologically a commonly used antibiotic with a very high safety record, minocycline, is also a potent microglial suppressant found to be neuroprotective in both spinal and cerebral trauma.<sup>[4]</sup> Another anti-inflammatory weapon is hyperbaric oxygen.<sup>[2]</sup> It markedly enhances wound healing and is approved for the treatment of brain abscesses because of its strong anti-inflammatory profile. Although not helpful in major brain injury, studies are now underway by the military to determine its efficacy in PCS.

In summary, we believe this important paper, although conservative in its tone, is one of the first to suggest what may become a paradigm shift in the treatment of post concussion syndrome. Rather than, or perhaps in conjunction with, antidepressants, anxiolytics, hypnotics and analgesics, omega 3 fatty acids, curcumin, creatine, catechins, minocycline and additionally vitamin D<sub>3</sub>, magnesium and hyperbaric oxygen to treat the underlying immunoexcitotoxicity may become the new treatment protocol for PCS. Obviously, further ongoing trials are needed but there are no significant “downsides” to any of these agents when used appropriately.

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