Surgical Neurology International

Review Article

Stuck at the bench: Potential natural neuroprotective compounds for concussion

Anthony L. Petraglia, Ethan A. Winkler[1], Julian E. Bailes[2]

Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, [1]University of Rochester School of Medicine and Dentistry, Rochester, NY, [2]Department of Neurosurgery, North Shore University Health System, Evanston, IL, USA

E-mail: *Anthony L. Petraglia - Anthony_Petraglia@urmc.rochester.edu; Ethan A. Winkler - Ethan_Winkler@urmc.rochester.edu; Julian E. Bailes - JBailes@northshore.org
*Corresponding author

Received: 29 August 11 Accepted: 22 September 11 Published: 12 October 11

This article may be cited as:
Petraglia AL, Winkler EA, Bailes JE. Stuck at the bench: Potential natural neuroprotective compounds for concussion. Surg Neurol Int 2011;2:146.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2011/2/1/146/85987

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

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.85987
Quick Response Code:

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.[139] 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.[15]

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.[15,141-143,168,173,186,210] Axonal transport can also be affected by delayed, progressive injury secondary to proteolysis.[94] At the cellular level, there is neuronal membrane disruption that leads to ionic shifts and an increase in intracellular glutamate and calcium.[15,102,141,168] 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.[15] Mitochondrial injury can also lead to failure in adenosine triphosphate (ATP) generation and an increase in reactive oxygen species.[225,243] Concussion may also compromise or alter the control of cerebral blood flow (CBF), cerebrovascular reactivity, and cerebral oxygenation.[121] 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.[25] 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.[62,190] Long-chain polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are highly enriched in neuronal synaptosomal plasma membranes and vesicles.[62] The predominant CNS polyunsaturated fatty acid is DHA which is readily retained in neuronal plasma membranes.[140] 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.[34,181] 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.[95] 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.[114,145,151]

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

Table 1: Eicosapentaenoic acid and docosahexaenoic acid mediated multi-mechanstic 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-1β and TNF-α	65
	Isolated monocytes	Fish oil	Decreased synthesis of TNF-α, 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-α, IL-6, NO synthase and COX-2 in microglia	133
Reduces excitoxicity				
	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.[32,34,35,65,85,132,133,144,148,170,181,193,208,228,237,238] [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;[81,91,153] however, such benefit has not been observed in all populations studied.[31] Randomized control trials have also demonstrated significant reductions in ischemic stroke recurrence,[217] relative risk for ischemic stroke,[2] and reduced incidence of both symptomatic vasospasm and mortality following subarachnoid hemorrhage.[253] Multiple studies, on the other hand, have found no statistically significant reduction in neurological impairment following ischemic stroke[72,172] reductions in epileptic seizure frequency.[28,57,174,255] Clinical trials in Alzheimer's disease have also been largely ineffective.[175] 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 Aryurvedic medicine.[73] More recently, curcumin has gained much attention from Western researchers for its potential therapeutic benefits in large part due to its potent anti-oxidant[128,194,236] and anti-inflammatory properties.[3,115,139] 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,[128,248] as well as acute neurological insults including ischemic stroke[61,93,203,221,247,259] and subarachnoid hemorrhage.[226]

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.[115,201,202,236,239] 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.[115,202,236] [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 1β and nuclear factor kappa B (NFκB). 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.[115]

Nonetheless, other studies have further evaluated the benefits of post-traumatic administration of a curcumin derivative, CNB-001, with enhanced neuroprotective properties.[131,201,239] 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,[201,239] 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.[16,59] 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-1β and peri-neuronal microgliosis	128
	Mouse TBI	Curcumin	Reduced expression of IL-1β and inhibited NFκB 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.[39] Another study has further suggested that increased curry consumption in an elderly population is associated with higher Mini Mental Status Examination scores.[159] In spite of these initial favorable findings, the results of more recent clinical trials in several Alzheimer's disease populations remain equivocal.[79] 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.[18] Since its original discovery in 1940, resveratrol has gained popular media attention for being the cardioprotective agent in red wine[26] and its capability of extending vertebrate lifespan.[17] Resveratrol has been demonstrated to effectively cross the blood-brain barrier and improve outcomes in animal models following multiple acute neurological insults including stroke,[70,88,123,176,206] global cerebral ischemia,[58] spinal cord injury,[99,111,249] and TBI.[11,205,209] Resveratrol has also been demonstrated to slow the development of chronic neurodegenerative disease in animal models.[101,179] Although many of resveratrol's therapeutic benefits are classically attributed to its potent anti-oxidant effects,[11,18] 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.[11,205,209] Resveratrol treatment in immature rodents reduced post-traumatic neuronal loss and improved behavioral measures of locomotion, anxiety, and novel object recognition memory.[209] 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 excitoxicity				
	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+/K+-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.[11] Furthermore, studies have demonstrated that resveratrol treatment reduces brain edema and lesion volume, as well as improves neurobehavioral functional performance following TBI.[11,205] 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[105] and reducing inflammation via inhibition of the pro-inflammatory molecule NFκB.[100] Epidemiological studies have also suggested that increased red wine consumption is associated with reductions in stroke risk.[155] 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.[19,161] 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.[19] 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.[19,241] More recent evidence also suggests that creatine may serve as a neuronal co-transmitter augmenting post-synaptic GABA signal transduction.[5,54,158,167] 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.[19,157]

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.[19,77] The neuroprotective effects may also be conferred in acute neurological injuries, such as TBI.[195,214] 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.[204] 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.[195,214] 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.[214] 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.[77,157] Acute supplementation of creatine may also improve cognition in elderly patients and adults following sleep deprivation.[146,147] Several studies have suggested that creatine supplementation may also reduce oxidative DNA damage and brain glutamate levels in Huntington disease patients.[21,84] 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.[22] 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.[188,189] 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.[188] 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.[188] 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.[189] Most important, creatine treatment appeared to be well tolerated and there were no significant side effects reported;[188,189] which was consistent with other human studies utilizing higher dosages.[10,22,84] While initial studies have also provided encouraging preliminary evidence supporting the use of creatine supplementation in the treatment of primary depression,[182] 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[14,78,97,106,108,138,178] [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,[156,212] and exerting neuroprotective benefits in animal models of peripheral nerve injury,[233] spinal cord trauma,[106] and ischemic stroke.[49,120,163] Epigallocatechin-3-gallate also displays neuroprotective properties in animal models of chronic neurodegenerative diseases including amyotrophic lateral sclerosis,[113,254] Parkinson's disease,[48,122,137] and Alzheimer's disease.[108,178] Epigallocatechin-3-gallate's neuroprotection has largely been attributed to its potent anti-oxidant[14,108,178,233] and anti-inflammatory properties;[106,138] 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,[63,97] Alzheimer's disease,[109] and Parkinson's disease.[43] Theanine, like EGCG, contains multiple mechanisms of neuroprotective action including protection from excitotoxic injury[97] and inhibition of inflammation[109] [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.[165]

Additional studies have also suggested that green tea extract may decrease cognitive decline in the elderly[160] and that L-theanine and theogallin-enriched green tea or caffeine may increase brain theta wave activity and performance on tasks requiring attention, respectively.[60,103] 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.[40] 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.[125] 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.[41] 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-α, IL-1β, COX-2	106
	Mouse ischemia	Theanine	Reduced post-ischemic microgliosis	63
	Mouse brain	Theanine	Inhibits activation of NFκB	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 factro	43
Synaptic transmission				
	Mouse ischemia	Theanine	Modulated post-synaptic GABAA receptors	63
Tau and amyloid-β				
	Alzheimer's mice	EGCG	Reduced tau phosphorylation and amyloid-β deposition	178

ECGC: Epigallocatechin-3-gallate

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

The preclinical evidence regarding the neuroprotective effects of caffeine administration in TBI is equivocal.[4,24,41,125,232] 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_1 receptors which, in turn, suppressed the synthesis of pro-inflammatory cytokines and reduced glutamate release and subsequent excitotoxic injury.[125] 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.[232] Other studies have demonstrated that selective adenosine A_1 agonists improve neuropathology following experimental injury,[224] whereas adenosine A_1 receptor genetic ablation worsens post-traumatic neuroinflammation and seizure activity.[80,112] 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.[24] Furthermore, the protective effects of post-traumatic caffeine administration were shown to be potentiated by its co-administration with alcohol.[56] 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.[4] 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,[192] Alzheimer's disease,[66,136,191] and Parkinson's disease;[9,53,183,185] 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.[216] 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.[117] However, in other populations chronic coffee intake has demonstrated no change in stroke risk[76] or in one study, even a transient increase in stroke risk immediately following ingestion.[152] Caffeine use has also been identified as a risk factor for subarachnoid hemorrhage[27] and intracerebral hemorrhage[69] 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;[20,50,180] 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.[187] While only a preliminary finding, this suggests that pre-traumatic caffeine ingestion may afford some degree of neuroprotection and improve outcomes following TBI.[187] 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.[51,87,177,240] 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-).[223] Vitamin E is a potent, lipid-soluble, anti-oxidant that is present in high concentrations in the mammalian brain.[211] In several animal models of brain injury such as ischemic stroke,[107,162] subarachnoid hemorrhage[104,222] and Alzheimer's disease,[215] 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.[87,240] 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.[51]

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;[52,196] whereas, others have failed to find such an association.[23,30,64,198] Additionally, several of these studies have noted an increased risk for hemorrhagic stroke, warranting caution for widespread usage.[196,198] While recent studies have reported that vitamin E supplementation in MCI and Alzheimer's disease patients has proven largely ineffective,[89] 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.[223] 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.[223] 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.[223]

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.[177] 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.[177] 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.[52] 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 hydroxlase responsible for vitamin D activation, but that multiple regions in the brain abundantly express the nuclear vitamin D receptor.[68] 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.[68]

Vitamin D deficiency is endemic in the adolescent, adult, and elderly populations in the United States,[38,75,220] and has been associated with inflammatory, autoimmune, cardiovascular, neuromuscular, and neurodegenerative diseases as well as cancer.[38] Population based studies have suggested that vitamin D deficiency in the elderly is indeed associated with an increased prevalence of Parkinson's disease[67] dementia, Alzheimer's disease, increased stroke risk and a higher prevalence of MRI findings suggestive of primary cerebrovascular lesions.[29] The association between vitamin D deficiency and elevated stroke risk or other cardiovascular disease has been confirmed in other studies.[6,171] Furthermore, a randomized controlled trial has suggested that post-ischemic administration of vitamin D may improve endothelial cell function.[234] These studies, albeit anecdotal, suggest that vitamin D may indeed posses 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 represents an important and necessary neuroprotective adjuvant for post-TBI progesterone therapy.[12,37,38] Progesterone is one of the few agents to demonstrate significant reductions in mortality following TBI in human patients in preliminary trials[235,242] 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.[12] Vitamin D deficiency may increase inflammatory damage and behavioral impairment following experimental injury and attenuate the protective effects of post-traumatic progesterone treatment.[37]

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,[71,82] whereas wogonin potently attenuates microglial activation and resultant neuroinflammation.[118,169] Independent studies have further demonstrated that baicalein and baicalin may also have anti-inflammatory properties through the inhibition of the proinflammatory molecule NFκB[213,246] and microglial activation.[124] Comparison studies have also demonstrated that baicalein may protect neurons from both excitoxic 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.[119] Other models have suggested that wogonin does promote neurite outgrowth[129] and indeed protects neurons from oxygen/glucose deprivation,[207] in addition to excitotoxic and oxidative injury.[44] Baicalein has been shown to protect neurons from endoplasmic stress-induced apoptosis as well.[47] 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,[45,86,110,199,200] cerebral reperfusion injury,[246] spinal cord injury,[36,256] Alzheimer's disease[134] and Parkinson's disease.[134,154] 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.[42] 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.[1,244] 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.[116,227,230] These compounds have been shown to reduce lipid peroxidation and mitochondrial permeability,[229,230] stabilize of intracellular calcium,[83] reduce neuroinflammation,[219] and protect the blood-brain barrier.[218,257] It's neuroprotective effects have been investigated in experimental models of stroke,[116,218] Parkinson's disease[230] and Alzheimer's disease.[130] 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[46,139] and anti-oxidant[90,166] 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.[90,166] Similarly, Pcynogenol administration, in a clinical study of elderly patients, led to improved cognition and reductions in markers of lipid peroxidase.[184]

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[258] and neuroinflammation,[96,231] protect mitochondrial function,[252] promote neurogenesis,[260] and promote expression of several neurotrophic factors.[127] In experimental models, ginsenosides and/or saponins have been demonstrated to exert protection in cerebral ischemia,[164] stroke,[250-252,260] subarachnoid hemorrhage,[126] Parkinson's disease[135] and Alzheimer's disease.[231] It is also is thought to protect cognitive function during aging.[258] Preclinical studies in at least one experimental model of TBI have suggested potential benefit in improving neuropathological and behavioral outcomes.[92] In humans, though, it remains unclear as to whether chronic administration of ginseng may improve cognition and/or slow progression of dementia.[74]

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.[25] 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.

REFERENCES

1. Danshen in ischemic stroke. Chin Med J (Engl) 1977;3:224-6.
2. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999;354:447-55.
3. Aggarwal BB, Shishodia S. Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: Reasoning for seasoning. Ann N Y Acad Sci 2004;1030:434-41.
4. Al Moutaery K, Al Deeb S, Ahmad Khan H, Tariq M. Caffeine impairs short-term neurological outcome after concussive head injury in rats. Neurosurgery 2003;53:704-11; discussion 711-2.
5. Almeida LS, Salomons GS, Hogenboom F, Jakobs C, Schoffelmeer AN. Exocytotic release of creatine in rat brain. Synapse 2006;60:118-23.
6. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, *et al*. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol 2010;106:963-8.
7. Arendash GW, Mori T, Cao C, Mamcarz M, Runfeldt M, Dickson A, *et al*. Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice. J Alzheimers Dis 2009;17:661-80.
8. Arendash GW, Schleif W, Rezai-Zadeh K, Jackson EK, Zacharia LC, Cracchiolo JR, *et al*. Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta-amyloid production. Neuroscience 2006;142:941-52.
9. Ascherio A, Zhang SM, Hernan MA, Kawachi I, Colditz GA, Speizer FE, *et al*. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol 2001;50:56-63.
10. Atassi N, Ratai EM, Greenblatt DJ, Pulley D, Zhao Y, Bombardier J, *et al*. A phase I, pharmacokinetic, dosage escalation study of creatine monohydrate in subjects with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 2010;11:508-13.
11. Ates O, Cayli S, Altinoz E, Gurses I, Yucel N, Sener M, *et al*. Neuroprotection by resveratrol against traumatic brain injury in rats. Mol Cell Biochem 2007;294:137-44.
12. Atif F, Sayeed I, Ishrat T, Stein DG. Progesterone with vitamin D affords better neuroprotection against excitotoxicity in cultured cortical neurons than progesterone alone. Mol Med 2009;15:328-36.
13. Bailes JE, Mills JD. Docosahexaenoic acid reduces traumatic axonal injury in a rodent head injury model. J Neurotrauma 2010;27:1617-24.
14. Baluchnejadmojarad T, Roghani M. Chronic epigallocatechin-3-gallate ameliorates learning and memory deficits in diabetic rats via modulation of nitric oxide and oxidative stress. Behav Brain Res 2011;224:305-10.
15. Barkhoudarian G, Hovda DA, Giza CC. The molecular pathophysiology of concussive brain injury. Clin Sports Med 2011;30:33-48, vii-iii.
16. Baum L, Cheung SK, Mok VC, Lam LC, Leung VP, Hui E, *et al*. Curcumin effects on blood lipid profile in a 6-month human study. Pharmacol Res 2007;56:509-14.
17. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, *et al*. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006;444:337-42.
18. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: The *in vivo* evidence. Nat Rev Drug Discov 2006;5:493-506.
19. Beard E, Braissant O. Synthesis and transport of creatine in the CNS: Importance for cerebral functions. J Neurochem 2010;115:297-313.
20. Bell MJ, Robertson CS, Kochanek PM, Goodman JC, Gopinath SP, Carcillo JA, *et al*. Interstitial brain adenosine and xanthine increase during jugular venous oxygen desaturations in humans after traumatic brain injury. Crit Care Med 2001;29:399-404.
21. Bender A, Auer DP, Merl T, Reilmann R, Saemann P, Yassouridis A, *et al*. Creatine supplementation lowers brain glutamate levels in Huntington's disease. J Neurol 2005;252:36-41.
22. Bender A, Koch W, Elstner M, Schombacher Y, Bender J, Moeschl M, *et al*. Creatine supplementation in Parkinson disease: A placebo-controlled randomized pilot trial. Neurology 2006;67:1262-4.
23. Bin Q, Hu X, Cao Y, Gao F. The role of vitamin E (tocopherol) supplementation in the prevention of stroke. A meta-analysis of 13 randomised controlled trials. Thromb Haemost 2011;105:579-85.
24. Blaha M, Vajnerova O, Bednar M, Vajner L, Tichy M. [Traumatic brain injuries--effects of alcohol and caffeine on intracranial pressure and cerebral blood flow]. Rozhl Chir 2009;88:682-6.
25. Blaylock RL, Maroon J. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy-A unifying hypothesis. Surg Neurol Int 2011;2:107.
26. Bradamante S, Barenghi L, Villa A. Cardiovascular protective effects of resveratrol. Cardiovasc Drug Rev 2004;22:169-88.
27. Broderick JP, Viscoli CM, Brott T, Kernan WN, Brass LM, Feldmann E, *et al*. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. Stroke 2003;34:1375-81.
28. Bromfield E, Dworetzky B, Hurwitz S, Eluri Z, Lane L, Replansky S, *et al*. A randomized trial of polyunsaturated fatty acids for refractory epilepsy. Epilepsy Behav 2008;12:187-90.
29. Buell JS, Dawson-Hughes B, Scott TM, Weiner DE, Dallal GE, Qui WQ, *et al*. 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. Neurology 2010;74:18-26.
30. Buring JE. Aspirin prevents stroke but not MI in women: Vitamin E has no effect on CV disease or cancer. Cleve Clin J Med 2006;73:863-70.
31. Caicoya M. Fish consumption and stroke: A community case-control study in Asturias, Spain. Neuroepidemiology 2002;21:107-14.
32. Calderon F, Kim HY. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. J Neurochem 2004;90:979-88.
33. Cao C, Cirrito JR, Lin X, Wang L, Verges DK, Dickson A, *et al*. Caffeine suppresses amyloid-beta levels in plasma and brain of Alzheimer's disease transgenic mice. J Alzheimers Dis 2009;17:681-97.
34. Cao D, Xue R, Xu J, Liu Z. Effects of docosahexaenoic acid on the survival and neurite outgrowth of rat cortical neurons in primary cultures. J Nutr Biochem 2005;16:538-46.
35. Cao DH, Xu JF, Xue RH, Zheng WF, Liu ZL. Protective effect of chronic ethyl docosahexaenoate administration on brain injury in ischemic gerbils. Pharmacol Biochem Behav 2004;79:651-9.
36. Cao Y, Li G, Wang YF, Fan ZK, Yu DS, Wang ZD, *et al*. Neuroprotective effect of baicalin on compression spinal cord injury in rats. Brain Res 2010;1357:115-23.
37. Cekic M, Cutler SM, Van Landingham JW, Stein DG. Vitamin D deficiency reduces the benefits of progesterone treatment after brain injury in aged rats. Neurobiol Aging 2011;32:864-74.
38. Cekic M, Stein DG. Traumatic brain injury and aging: Is a combination of progesterone and vitamin D hormone a simple solution to a complex problem? Neurotherapeutics 2010;7:81-90.

39. Chandra V, Pandav R, Dodge HH, Johnston JM, Belle SH, De Kosky ST, *et al*. Incidence of Alzheimer's disease in a rural community in India: The Indo-US study. Neurology 2001;57:985-9.
40. Checkoway H, Powers K, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. Am J Epidemiol 2002;155:732-8.
41. Chen JF, Chern Y. Impacts of methylxanthines and adenosine receptors on neurodegeneration: Human and experimental studies. Handb Exp Pharmacol 2011:267-310.
42. Chen SF, Hsu CW, Huang WH, Wang JY. Post-injury baicalein improves histological and functional outcomes and reduces inflammatory cytokines after experimental traumatic brain injury. Br J Pharmacol 2008;155:1279-96.
43. Cho HS, Kim S, Lee SY, Park JA, Kim SJ, Chun HS. Protective effect of the green tea component, L-theanine on environmental toxins-induced neuronal cell death. Neurotoxicology 2008;29:656-62.
44. Cho J, Lee HK. Wogonin inhibits excitotoxic and oxidative neuronal damage in primary cultured rat cortical cells. Eur J Pharmacol 2004;485:105-10.
45. Cho J, Lee HK. Wogonin inhibits ischemic brain injury in a rat model of permanent middle cerebral artery occlusion. Biol Pharm Bull 2004;27:1561-4.
46. Cho KJ, Yun CH, Yoon DY, Cho YS, Rimbach G, Packer L, *et al*. Effect of bioflavonoids extracted from the bark of Pinus maritima on proinflammatory cytokine interleukin-1 production in lipopolysaccharide-stimulated RAW 264.7. Toxicol Appl Pharmacol 2000;168:64-71.
47. Choi JH, Choi AY, Yoon H, Choe W, Yoon KS, Ha J, *et al*. Baicalein protects HT22 murine hippocampal neuronal cells against endoplasmic reticulum stress-induced apoptosis through inhibition of reactive oxygen species production and CHOP induction. Exp Mol Med 2010;42:811-22.
48. Choi JY, Park CS, Kim DJ, Cho MH, Jin BK, Pie JE, *et al*. Prevention of nitric oxide-mediated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice by tea phenolic epigallocatechin 3-gallate. Neurotoxicology 2002;23:367-74.
49. Choi YB, Kim YI, Lee KS, Kim BS, Kim DJ. Protective effect of epigallocatechin gallate on brain damage after transient middle cerebral artery occlusion in rats. Brain Res 2004;1019:47-54.
50. Clark RS, Carcillo JA, Kochanek PM, Obrist WD, Jackson EK, Mi Z, *et al*. Cerebrospinal fluid adenosine concentration and uncoupling of cerebral blood flow and oxidative metabolism after severe head injury in humans. Neurosurgery 1997;41:1284-92; discussion 1292-3.
51. Conte V, Uryu K, Fujimoto S, Yao Y, Rokach J, Longhi L, *et al*. Vitamin E reduces amyloidosis and improves cognitive function in Tg2576 mice following repetitive concussive brain injury. J Neurochem 2004;90:758-64.
52. Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, *et al*. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: Results from the Women's Antioxidant Cardiovascular Study. Arch Intern Med 2007;167:1610-8.
53. Costa J, Lunet N, Santos C, Santos J, Vaz-Carneiro A. Caffeine exposure and the risk of Parkinson's disease: A systematic review and meta-analysis of observational studies. J Alzheimers Dis 2010;20 Suppl 1:S221-38.
54. Cupello A, Balestrino M, Gatta E, Pellistri F, Siano S, Robello M. Activation of cerebellar granule cells GABA(A) receptors by guanidinoacetate. Neuroscience 2008;152:65-9.
55. Dall'Igna OP, Porciuncula LO, Souza DO, Cunha RA, Lara DR. Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amyloid neurotoxicity. Br J Pharmacol 2003;138:1207-9.
56. Dash PK, Moore AN, Moody MR, Treadwell R, Felix JL, Clifton GL. Post-trauma administration of caffeine plus ethanol reduces contusion volume and improves working memory in rats. J Neurotrauma 2004;21:1573-83.
57. De Giorgio CM, Miller P, Meymandi S, Gornbein JA. n-3 fatty acids (fish oil) for epilepsy, cardiac risk factors, and risk of SUDEP: Clues from a pilot, double-blind, exploratory study. Epilepsy Behav 2008;13:681-4.
58. Della-Morte D, Dave KR, DeFazio RA, Bao YC, Raval AP, Perez-Pinzon MA. Resveratrol pretreatment protects rat brain from cerebral ischemic damage via a sirtuin 1-uncoupling protein 2 pathway. Neuroscience 2009;159:993-1002.
59. Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, *et al*. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res 2008;14:4491-9.
60. Dimpfel W, Kler A, Kriesl E, Lehnfeld R, Keplinger-Dimpfel IK. Source density analysis of the human EEG after ingestion of a drink containing decaffeinated extract of green tea enriched with L-theanine and theogallin. Nutr Neurosci 2007;10:169-80.
61. Dohare P, Garg P, Jain V, Nath C, Ray M. Dose dependence and therapeutic window for the neuroprotective effects of curcumin in thromboembolic model of rat. Behav Brain Res 2008;193:289-97.
62. Dyall SC, Michael-Titus AT. Neurological benefits of omega-3 fatty acids. Neuromolecular Med 2008;10:219-35.
63. Egashira N, Hayakawa K, Osajima M, Mishima K, Iwasaki K, Oishi R, *et al*. Involvement of GABA(A) receptors in the neuroprotective effect of theanine on focal cerebral ischemia in mice. J Pharmacol Sci 2007;105:211-4.
64. Eidelman RS, Hollar D, Hebert PR, Lamas GA, Hennekens CH. Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. Arch Intern Med 2004;164:1552-6.
65. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JW, *et al*. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265-71.
66. Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M. Midlife coffee and tea drinking and the risk of late-life dementia: A population-based CAIDE study. J Alzheimers Dis 2009;16:85-91.
67. Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of vitamin d insufficiency in patients with Parkinson disease and Alzheimer disease. Arch Neurol 2008;65:1348-52.
68. Eyles D, Burne T, McGrath J. Vitamin D in fetal brain development. Semin Cell Dev Biol 2011 [In press].
69. Feldmann E, Broderick JP, Kernan WN, Viscoli CM, Brass LM, Brott T, *et al*. Major risk factors for intracerebral hemorrhage in the young are modifiable. Stroke 2005;36:1881-5.
70. Gao D, Zhang X, Jiang X, Peng Y, Huang W, Cheng G, *et al*. Resveratrol reduces the elevated level of MMP-9 induced by cerebral ischemia-reperfusion in mice. Life Sci 2006;78:2564-70.
71. Gao Z, Huang K, Yang X, Xu H. Free radical scavenging and antioxidant activities of flavonoids extracted from the radix of *Scutellaria baicalensis* Georgi. Biochim Biophys Acta 1999;1472:643-50.
72. Garbagnati F, Cairella G, De Martino A, Multari M, Scognamiglio U, Venturiero V, *et al*. Is antioxidant and n-3 supplementation able to improve functional status in poststroke patients? Results from the Nutristroke Trial. Cerebrovasc Dis 2009;27:375-83.
73. Garodia P, Ichikawa H, Malani N, Sethi G, Aggarwal BB. From ancient medicine to modern medicine: Ayurvedic concepts of health and their role in inflammation and cancer. J Soc Integr Oncol 2007;5:25-37.
74. Geng J, Dong J, Ni H, Lee MS, Wu T, Jiang K, *et al*. Ginseng for cognition. Cochrane Database Syst Rev 2010:CD007769.
75. Gordon CM, De Peter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004;158:531-7.
76. Grobbee DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willett W. Coffee, caffeine, and cardiovascular disease in men. N Engl J Med 1990;323:1026-32.
77. Gualano B, Artioli GG, Poortmans JR, Lancha Junior AH. Exploring the therapeutic role of creatine supplementation. Amino Acids 2010;38:31-44.
78. Gundimeda U, McNeill TH, Schiffman JE, Hinton DR, Gopalakrishna R. Green tea polyphenols potentiate the action of nerve growth factor to induce neuritogenesis: Possible role of reactive oxygen species. J Neurosci Res 2010;88:3644-55.
79. Hamaguchi T, Ono K, Yamada M. Review: Curcumin and Alzheimer's disease. CNS Neurosci Ther 2010;16:285-97.
80. Haselkorn ML, Shellington DK, Jackson EK, Vagni VA, Janesko-Feldman K, Dubey RK, *et al*. Adenosine A1 receptor activation as a brake on the microglial response after experimental traumatic brain injury in mice. J Neurotrauma 2010;27:901-10.
81. He K, Rimm EB, Merchant A, Rosner BA, Stampfer MJ, Willett WC, *et al*. Fish consumption and risk of stroke in men. JAMA 2002;288:3130-6.
82. He XL, Wang YH, Gao M, Li XX, Zhang TT, Du GH. Baicalein protects rat brain mitochondria against chronic cerebral hypoperfusion-induced oxidative damage. Brain Res 2009;1249:212-21.
83. Hei M, Luo Y, Zhang X, Liu F. Tanshinone IIa alleviates the biochemical changes associated with hypoxic ischemic brain damage in a rat model. Phytother Res 2011[In press].

84. Hersch SM, Gevorkian S, Marder K, Moskowitz C, Feigin A, Cox M, *et al*. Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. Neurology 2006;66:250-2.
85. Hogyes E, Nyakas C, Kiliaan A, Farkas T, Penke B, Luiten PG. Neuroprotective effect of developmental docosahexaenoic acid supplement against excitotoxic brain damage in infant rats. Neuroscience 2003;119:999-1012.
86. Hwang YK, Jinhua M, Choi BR, Cui CA, Jeon WK, Kim H, *et al*. Effects of *Scutellaria baicalensis* on chronic cerebral hypoperfusion-induced memory impairments and chronic lipopolysaccharide infusion-induced memory impairments. J Ethnopharmacol 2011;137:681-9.
87. Inci S, Ozcan OE, Kilinc K. Time-level relationship for lipid peroxidation and the protective effect of alpha-tocopherol in experimental mild and severe brain injury. Neurosurgery 1998;43:330-5; discussion 335-6.
88. Inoue H, Jiang XF, Katayama T, Osada S, Umesono K, Namura S. Brain protection by resveratrol and fenofibrate against stroke requires peroxisome proliferator-activated receptor alpha in mice. Neurosci Lett 2003;352:203-6.
89. Isaac MG, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2008:CD002854.
90. Ishrat T, Parveen K, Hoda MN, Khan MB, Yousuf S, Ansari MA, *et al*. Effects of Pycnogenol and vitamin E on cognitive deficits and oxidative damage induced by intracerebroventricular streptozotocin in rats. Behav Pharmacol 2009;20:567-75.
91. Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, *et al*. Intake of fish and omega-3 fatty acids and risk of stroke in women. JAMA 2001;285:304-12.
92. Ji YC, Kim YB, Park SW, Hwang SN, Min BK, Hong HJ, *et al*. Neuroprotective effect of ginseng total saponins in experimental traumatic brain injury. J Korean Med Sci 2005;20:291-6.
93. Jiang J, Wang W, Sun YJ, Hu M, Li F, Zhu DY. Neuroprotective effect of curcumin on focal cerebral ischemic rats by preventing blood-brain barrier damage. Eur J Pharmacol 2007;561:54-62.
94. Johnson GV, Greenwood JA, Costello AC, Troncoso JC. The regulatory role of calmodulin in the proteolysis of individual neurofilament proteins by calpain. Neurochem Res 1991;16:869-73.
95. Jones PJ, Kubow K. Lipids, sterols, and their metabolites. In Shils ME, Shike, M, Ross AC, *et al*, eds. Modern Nutrition in Health and Disease, 10th edition. Philadelphia: Lippincott Williams & Wilkins, 2005:110-114.
96. Jung JS, Shin JA, Park EM, Lee JE, Kang YS, Min SW, *et al*. Anti-inflammatory mechanism of ginsenoside Rh1 in lipopolysaccharide-stimulated microglia: Critical role of the protein kinase A pathway and hemeoxygenase-1 expression. J Neurochem 2010;115:1668-80.
97. Kakuda T, Yanase H, Utsunomiya K, Nozawa A, Unno T, Kataoka K. Protective effect of gamma-glutamylethylamide (theanine) on ischemic delayed neuronal death in gerbils. Neurosci Lett 2000;289:189-92.
98. Kalda A, Yu L, Oztas E, Chen JF. Novel neuroprotection by caffeine and adenosine A(2A) receptor antagonists in animal models of Parkinson's disease. J Neurol Sci 2006;248:9-15.
99. Kaplan S, Bisleri G, Morgan JA, Cheema FH, Oz MC. Resveratrol, a natural red wine polyphenol, reduces ischemia-reperfusion-induced spinal cord injury. Ann Thorac Surg 2005;80:2242-9.
100. Karlsen A, Paur I, Bohn SK, Sakhi AK, Borge GI, Serafini M, *et al*. Bilberry juice modulates plasma concentration of NF-kappaB related inflammatory markers in subjects at increased risk of CVD. Eur J Nutr 2010;49:345-55.
101. Karuppagounder SS, Pinto JT, Xu H, Chen HL, Beal MF, Gibson GE. Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. Neurochem Int 2009;54:111-8.
102. Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. J Neurosurg 1990;73:889-900.
103. Kelly SP, Gomez-Ramirez M, Montesi JL, Foxe JJ. L-theanine and caffeine in combination affect human cognition as evidenced by oscillatory alpha-band activity and attention task performance. J Nutr 2008;138:1572S-7.
104. Kemaloglu S, Ozkan U, Yilmaz F, Ak E, Acemoglu H, Olmez G, *et al*. Preventive effects of intracisternal alphatochopherol on cerebral vasospasm in experimental subarachnoid haemorrhage. Yonsei Med J 2003;44:955-60.
105. Kennedy DO, Wightman EL, Reay JL, Lietz G, Okello EJ, Wilde A, *et al*. Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: A double-blind, placebo-controlled, crossover investigation. Am J Clin Nutr 2010;91:1590-7.
106. Khalatbary AR, Ahmadvand H. Anti-inflammatory effect of the epigallocatechin gallate following spinal cord trauma in rat. Iran Biomed J 2011;15:31-7.
107. Khanna S, Roy S, Slivka A, Craft TK, Chaki S, Rink C, *et al*. Neuroprotective properties of the natural vitamin E alpha-tocotrienol. Stroke 2005;36:2258-64.
108. Kim J, Lee HJ, Lee KW. Naturally occurring phytochemicals for the prevention of Alzheimer's disease. J Neurochem 2010;112:1415-30.
109. Kim TI, Lee YK, Park SG, Choi IS, Ban JO, Park HK, *et al*. l-Theanine, an amino acid in green tea, attenuates beta-amyloid-induced cognitive dysfunction and neurotoxicity: Reduction in oxidative damage and inactivation of ERK/p38 kinase and NF-kappaB pathways. Free Radic Biol Med 2009;47:1601-10.
110. Kim YO, Leem K, Park J, Lee P, Ahn DK, Lee BC, *et al*. Cytoprotective effect of *Scutellaria baicalensis* in CA1 hippocampal neurons of rats after global cerebral ischemia. J Ethnopharmacol 2001;77:183-8.
111. Kiziltepe U, Turan NN, Han U, Ulus AT, Akar F. Resveratrol, a red wine polyphenol, protects spinal cord from ischemia-reperfusion injury. J Vasc Surg 2004;40:138-45.
112. Kochanek PM, Vagni VA, Janesko KL, Washington CB, Crumrine PK, Garman RH, *et al*. Adenosine A1 receptor knockout mice develop lethal status epilepticus after experimental traumatic brain injury. J Cereb Blood Flow Metab 2006;26:565-75.
113. Koh SH, Lee SM, Kim HY, Lee KY, Lee YJ, Kim HT, *et al*. The effect of epigallocatechin gallate on suppressing disease progression of ALS model mice. Neurosci Lett 2006;395:103-7.
114. Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, *et al*. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res 2006;56:159-64.
115. Laird MD, Sukumari-Ramesh S, Swift AE, Meiler SE, Vender JR, Dhandapani KM. Curcumin attenuates cerebral edema following traumatic brain injury in mice: A possible role for aquaporin-4? J Neurochem 2010;113:637-48.
116. Lam BY, Lo AC, Sun X, Luo HW, Chung SK, Sucher NJ. Neuroprotective effects of tanshinones in transient focal cerebral ischemia in mice. Phytomedicine 2003;10:286-91.
117. Larsson SC, Virtamo J, Wolk A. Coffee consumption and risk of stroke in women. Stroke 2011;42:908-12.
118. Lee H, Kim YO, Kim H, Kim SY, Noh HS, Kang SS, *et al*. Flavonoid wogonin from medicinal herb is neuroprotective by inhibiting inflammatory activation of microglia. FASEB J 2003;17:1943-4.
119. Lee HH, Yang LL, Wang CC, Hu SY, Chang SF, Lee YH. Differential effects of natural polyphenols on neuronal survival in primary cultured central neurons against glutamate- and glucose deprivation-induced neuronal death. Brain Res 2003;986:103-13.
120. Lee SY, Kim CY, Lee JJ, Jung JG, Lee SR. Effects of delayed administration of (-)-epigallocatechin gallate, a green tea polyphenol on the changes in polyamine levels and neuronal damage after transient forebrain ischemia in gerbils. Brain Res Bull 2003;61:399-406.
121. Len TK, Neary JP. Cerebrovascular pathophysiology following mild traumatic brain injury. Clin Physiol Funct Imaging 2011;31:85-93.
122. Levites Y, Weinreb O, Maor G, Youdim MB, Mandel S. Green tea polyphenol (-)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration. J Neurochem 2001;78:1073-82.
123. Li C, Yan Z, Yang J, Chen H, Li H, Jiang Y, *et al*. Neuroprotective effects of resveratrol on ischemic injury mediated by modulating the release of neurotransmitter and neuromodulator in rats. Neurochem Int 2010;56:495-500.
124. Li FQ, Wang T, Pei Z, Liu B, Hong JS. Inhibition of microglial activation by the herbal flavonoid baicalein attenuates inflammation-mediated degeneration of dopaminergic neurons. J Neural Transm 2005;112:331-47.
125. Li W, Dai S, An J, Li P, Chen X, Xiong R, *et al*. Chronic but not acute treatment with caffeine attenuates traumatic brain injury in the mouse cortical impact model. Neuroscience 2008;151:1198-207.
126. Li Y, Tang J, Khatibi NH, Zhu M, Chen D, Tu L, *et al*. Treatment with ginsenoside rb1, a component of panax ginseng, provides neuroprotection in rats subjected to subarachnoid hemorrhage-induced brain injury. Acta Neurochir Suppl 2011;110:75-9.
127. Liang W, Ge S, Yang L, Yang M, Ye Z, Yan M, *et al*. Ginsenosides Rb1 and Rg1 promote proliferation and expression of neurotrophic factors in primary Schwann cell cultures. Brain Res 2010;1357:19-25.
128. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice

curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 2001;21:8370-7.
129. Lim JS, Yoo M, Kwon HJ, Kim H, Kwon YK. Wogonin induces differentiation and neurite outgrowth of neural precursor cells. Biochem Biophys Res Commun 2010;402:42-7.
130. Liu T, Jin H, Sun QR, Xu JH, Hu HT. The neuroprotective effects of tanshinone IIA on beta-amyloid-induced toxicity in rat cortical neurons. Neuropharmacology 2010;59:595-604.
131. Liu Y, Dargusch R, Maher P, Schubert D. A broadly neuroprotective derivative of curcumin. J Neurochem 2008;105:1336-45.
132. Lonergan PE, Martin DS, Horrobin DF, Lynch MA. Neuroprotective actions of eicosapentaenoic acid on lipopolysaccharide-induced dysfunction in rat hippocampus. J Neurochem 2004;91:20-9.
133. Lu DY, Tsao YY, Leung YM, Su KP. Docosahexaenoic acid suppresses neuroinflammatory responses and induces heme oxygenase-1 expression in BV-2 microglia: Implications of antidepressant effects for omega-3 fatty acids. Neuropsychopharmacology 2010;35:2238-48.
134. Lu JH, Ardah MT, Durairajan SS, Liu LF, Xie LX, Fong WF, *et al*. Baicalein inhibits formation of alpha-synuclein oligomers within living cells and prevents abeta peptide fibrillation and oligomerisation. Chembiochem 2011[In press].
135. Luo FC, Wang SD, Qi L, Song JY, Lv T, Bai J. Protective effect of panaxatriol saponins extracted from Panax notoginseng against MPTP-induced neurotoxicity *in vivo*. J Ethnopharmacol 2011;133:448-53.
136. Maia L, de Mendonca A. Does caffeine intake protect from Alzheimer's disease? Eur J Neurol 2002;9:377-82.
137. Mandel S, Maor G, Youdim MB. Iron and alpha-synuclein in the substantia nigra of MPTP-treated mice: Effect of neuroprotective drugs R-apomorphine and green tea polyphenol (-)-epigallocatechin-3-gallate. J Mol Neurosci 2004;24:401-16.
138. Mandel S, Weinreb O, Amit T, Youdim MB. Cell signaling pathways in the neuroprotective actions of the green tea polyphenol (-)-epigallocatechin-3-gallate: Implications for neurodegenerative diseases. J Neurochem 2004;88:1555-69.
139. Maroon JC, Bost JW, Maroon A. Natural anti-inflammatory agents for pain relief. Surg Neurol Int 2010;1:80.
140. Martinez M. Tissue levels of polyunsaturated fatty acids during early human development. J Pediatr 1992;120:S129-38.
141. Mata M, Staple J, Fink DJ. Changes in intra-axonal calcium distribution following nerve crush. J Neurobiol 1986;17:449-67.
142. Maxwell WL, McCreath BJ, Graham DI, Gennarelli TA. Cytochemical evidence for redistribution of membrane pump calcium-ATPase and ecto-Ca-ATPase activity, and calcium influx in myelinated nerve fibres of the optic nerve after stretch injury. J Neurocytol 1995;24:925-42.
143. Maxwell WL, Povlishock JT, Graham DL. A mechanistic analysis of nondisruptive axonal injury: A review. J Neurotrauma 1997;14:419-40.
144. Mayer K, Meyer S, Reinholz-Muhly M, Maus U, Merfels M, Lohmeyer J, *et al*. Short-time infusion of fish oil-based lipid emulsions, approved for parenteral nutrition, reduces monocyte proinflammatory cytokine generation and adhesive interaction with endothelium in humans. J Immunol 2003;171:4837-43.
145. McGahon BM, Martin DS, Horrobin DF, Lynch MA. Age-related changes in synaptic function: Analysis of the effect of dietary supplementation with omega-3 fatty acids. Neuroscience 1999;94:305-14.
146. McMorris T, Harris RC, Howard AN, Langridge G, Hall B, Corbett J, *et al*. Creatine supplementation, sleep deprivation, cortisol, melatonin and behavior. Physiol Behav 2007;90:21-8.
147. McMorris T, Mielcarz G, Harris RC, Swain JP, Howard A. Creatine supplementation and cognitive performance in elderly individuals. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2007;14:517-28.
148. Menard C, Patenaude C, Gagne AM, Massicotte G. AMPA receptor-mediated cell death is reduced by docosahexaenoic acid but not by eicosapentaenoic acid in area CA1 of hippocampal slice cultures. J Neurosci Res 2009;87:876-86.
149. Mills JD, Bailes JE, Sedney CL, Hutchins H, Sears B. Omega-3 fatty acid supplementation and reduction of traumatic axonal injury in a rodent head injury model. J Neurosurg 2011;114:77-84.
150. Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. Neurosurgery 2011;68:474-81; discussion 481.
151. Morley JE, Banks WA. Lipids and cognition. J Alzheimers Dis 2010;20:737-47.
152. Mostofsky E, Schlaug G, Mukamal KJ, Rosamond WD, Mittleman MA. Coffee and acute ischemic stroke onset: The Stroke Onset Study. Neurology 2010;75:1583-8.
153. Mozaffarian D, Longstreth WT Jr, Lemaitre RN, Manolio TA, Kuller LH, Burke GL, *et al*. Fish consumption and stroke risk in elderly individuals: The cardiovascular health study. Arch Intern Med 2005;165:200-6.
154. Mu X, He G, Cheng Y, Li X, Xu B, Du G. Baicalein exerts neuroprotective effects in 6-hydroxydopamine-induced experimental parkinsonism *in vivo* and *in vitro*. Pharmacol Biochem Behav 2009;92:642-8.
155. Mukamal KJ, Ascherio A, Mittleman MA, Conigrave KM, Camargo CA Jr, Kawachi I, *et al*. Alcohol and risk for ischemic stroke in men: The role of drinking patterns and usual beverage. Ann Intern Med 2005;142:11-9.
156. Nakagawa K, Miyazawa T. Absorption and distribution of tea catechin, (-)-epigallocatechin-3-gallate, in the rat. J Nutr Sci Vitaminol (Tokyo) 1997;43:679-84.
157. Nasrallah F, Feki M, Kaabachi N. Creatine and creatine deficiency syndromes: Biochemical and clinical aspects. Pediatr Neurol 2010;42:163-71.
158. Neu A, Neuhoff H, Trube G, Fehr S, Ullrich K, Roeper J, *et al*. Activation of GABA(A) receptors by guanidinoacetate: A novel pathophysiological mechanism. Neurobiol Dis 2002;11:298-307.
159. Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH. Curry consumption and cognitive function in the elderly. Am J Epidemiol 2006;164:898-906.
160. Ng TP, Feng L, Niti M, Kua EH, Yap KB. Tea consumption and cognitive impairment and decline in older Chinese adults. Am J Clin Nutr 2008;88:224-31.
161. Ohtsuki S, Tachikawa M, Takanaga H, Shimizu H, Watanabe M, Hosoya K, *et al*. The blood-brain barrier creatine transporter is a major pathway for supplying creatine to the brain. J Cereb Blood Flow Metab 2002;22:1327-35.
162. Park HA, Kubicki N, Gnyawali S, Chan YC, Roy S, Khanna S, *et al*. Natural vitamin E {alpha}-tocotrienol protects against ischemic stroke by induction of multidrug resistance-associated protein 1. Stroke 2011;42:2308-14.
163. Park JW, Hong JS, Lee KS, Kim HY, Lee JJ, Lee SR. Green tea polyphenol (-)-epigallocatechin gallate reduces matrix metalloproteinase-9 activity following transient focal cerebral ischemia. J Nutr Biochem 2010;21:1038-44.
164. Park SI, Jang DK, Han YM, Sunwoo YY, Park MS, Chung YA, *et al*. Effect of combination therapy with sodium ozagrel and panax ginseng on transient cerebral ischemia model in rats. J Biomed Biotechnol 2010;2010:893401.
165. Park SK, Jung IC, Lee WK, Lee YS, Park HK, Go HJ, *et al*. A combination of green tea extract and l-theanine improves memory and attention in subjects with mild cognitive impairment: A double-blind placebo-controlled study. J Med Food 2011;14:334-43.
166. Peng QL, Buz'Zard AR, Lau BH. Pycnogenol protects neurons from amyloid-beta peptide-induced apoptosis. Brain Res Mol Brain Res 2002;104:55-65.
167. Peral MJ, Vazquez-Carretero MD, Ilundain AA. Na(+)/Cl(-)/creatine transporter activity and expression in rat brain synaptosomes. Neuroscience 2010;165:53-60.
168. Pettus EH, Povlishock JT. Characterization of a distinct set of intra-axonal ultrastructural changes associated with traumatically induced alteration in axolemmal permeability. Brain Res 1996;722:1-11.
169. Piao HZ, Jin SA, Chun HS, Lee JC, Kim WK. Neuroprotective effect of wogonin: Potential roles of inflammatory cytokines. Arch Pharm Res 2004;27:930-6.
170. Pifferi F, Jouin M, Alessandri JM, Haedke U, Roux F, Perriere N, *et al*. n-3 Fatty acids modulate brain glucose transport in endothelial cells of the blood-brain barrier. Prostaglandins Leukot Essent Fatty Acids 2007;77:279-86.
171. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, *et al*. Low vitamin d levels predict stroke in patients referred to coronary angiography. Stroke 2008;39:2611-3.
172. Poppitt SD, Howe CA, Lithander FE, Silvers KM, Lin RB, Croft J, *et al*. Effects of moderate-dose omega-3 fish oil on cardiovascular risk factors and mood after ischemic stroke: A randomized, controlled trial. Stroke 2009;40:3485-92.
173. Povlishock JT, Pettus EH. Traumatically induced axonal damage: Evidence for enduring changes in axolemmal permeability with associated cytoskeletal change. Acta Neurochir Suppl 1996;66:81-6.
174. Puri BK, Koepp MJ, Holmes J, Hamilton G, Yuen AW. A 31-phosphorus neurospectroscopy study of omega-3 long-chain polyunsaturated fatty acid intervention with eicosapentaenoic acid and docosahexaenoic acid in patients with chronic refractory epilepsy. Prostaglandins Leukot Essent Fatty Acids 2007;77:105-7.

175. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, *et al*. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: A randomized trial. JAMA 2010;304:1903-11.
176. Raval AP, Dave KR, Perez-Pinzon MA. Resveratrol mimics ischemic preconditioning in the brain. J Cereb Blood Flow Metab 2006;26:1141-7.
177. Razmkon A, Sadidi A, Sherafat-Kazemzadeh E, Mehrafshan A, Bakhtazad A. Beneficial effects of vitamin c and vitamin e administration in severe head injury: A randomized double-blind control trial. Paper presented at Congress of Neurological Surgeons Annual Meeting, San Francisco, CA; 2010.
178. Rezai-Zadeh K, Arendash GW, Hou H, Fernandez F, Jensen M, Runfeldt M, *et al*. Green tea epigallocatechin-3-gallate (EGCG) reduces beta-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice. Brain Res 2008;1214:177-87.
179. Richard T, Pawlus AD, Iglesias ML, Pedrot E, Waffo-Teguo P, Merillon JM, *et al*. Neuroprotective properties of resveratrol and derivatives. Ann N Y Acad Sci 2011;1215:103-8.
180. Robertson CL, Bell MJ, Kochanek PM, Adelson PD, Ruppel RA, Carcillo JA, *et al*. Increased adenosine in cerebrospinal fluid after severe traumatic brain injury in infants and children: Association with severity of injury and excitotoxicity. Crit Care Med 2001;29:2287-93.
181. Robson LG, Dyall S, Sidloff D, Michael-Titus AT. Omega-3 polyunsaturated fatty acids increase the neurite outgrowth of rat sensory neurones throughout development and in aged animals. Neurobiol Aging 2010;31:678-87.
182. Roitman S, Green T, Osher Y, Karni N, Levine J. Creatine monohydrate in resistant depression: A preliminary study. Bipolar Disord 2007;9:754-8.
183. Ross GW, Petrovitch H. Current evidence for neuroprotective effects of nicotine and caffeine against Parkinson's disease. Drugs Aging 2001;18: 797-806.
184. Ryan J, Croft K, Mori T, Wesnes K, Spong J, Downey L, *et al*. An examination of the effects of the antioxidant Pycnogenol on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population. J Psychopharmacol 2008;22:553-62.
185. Saaksjarvi K, Knekt P, Rissanen H, Laaksonen MA, Reunanen A, Mannisto S. Prospective study of coffee consumption and risk of Parkinson's disease. Eur J Clin Nutr 2008;62:908-15.
186. Saatman KE, Abai B, Grosvenor A, Vorwerk CK, Smith DH, Meaney DF. Traumatic axonal injury results in biphasic calpain activation and retrograde transport impairment in mice. J Cereb Blood Flow Metab 2003;23:34-42.
187. Sachse KT, Jackson EK, Wisniewski SR, Gillespie DG, Puccio AM, Clark RS, *et al*. Increases in cerebrospinal fluid caffeine concentration are associated with favorable outcome after severe traumatic brain injury in humans. J Cereb Blood Flow Metab 2008;28:395-401.
188. Sakellaris G, Kotsiou M, Tamiolaki M, Kalostos G, Tsapaki E, Spanaki M, *et al*. Prevention of complications related to traumatic brain injury in children and adolescents with creatine administration: An open label randomized pilot study. J Trauma 2006;61:322-9.
189. Sakellaris G, Nasis G, Kotsiou M, Tamiolaki M, Charissis G, Evangeliou A. Prevention of traumatic headache, dizziness and fatigue with creatine administration. A pilot study. Acta Paediatr 2008;97:31-4.
190. Salem N Jr, Litman B, Kim HY, Gawrisch K. Mechanisms of action of docosahexaenoic acid in the nervous system. Lipids 2001;36:945-59.
191. Santos C, Costa J, Santos J, Vaz-Carneiro A, Lunet N. Caffeine intake and dementia: Systematic review and meta-analysis. J Alzheimers Dis 2010;20 Suppl 1:S187-204.
192. Santos C, Lunet N, Azevedo A, de Mendonca A, Ritchie K, Barros H. Caffeine intake is associated with a lower risk of cognitive decline: A cohort study from Portugal. J Alzheimers Dis 2010;20 Suppl 1:S175-85.
193. Sarsilmaz M, Songur A, Ozyurt H, Kus I, Ozen OA, Ozyurt B, *et al*. Potential role of dietary omega-3 essential fatty acids on some oxidant/antioxidant parameters in rats' corpus striatum. Prostaglandins Leukot Essent Fatty Acids 2003;69:253-9.
194. Scapagnini G, Caruso C, Calabrese V. Therapeutic potential of dietary polyphenols against brain ageing and neurodegenerative disorders. Adv Exp Med Biol 2010;698:27-35.
195. Scheff SW, Dhillon HS. Creatine-enhanced diet alters levels of lactate and free fatty acids after experimental brain injury. Neurochem Res 2004;29:469-79.
196. Schurks M, Glynn RJ, Rist PM, Tzourio C, Kurth T. Effects of vitamin E on stroke subtypes: Meta-analysis of randomised controlled trials. BMJ 2010;341:c5702.
197. Schwarzschild MA, Xu K, Oztas E, Petzer JP, Castagnoli K, Castagnoli N Jr, *et al*. Neuroprotection by caffeine and more specific A2A receptor antagonists in animal models of Parkinson's disease. Neurology 2003;61 Suppl 6:S55-61.
198. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, *et al*. Vitamins E and C in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. JAMA 2008;300: 2123-33.
199. Shang Y, Cheng J, Qi J, Miao H. Scutellaria flavonoid reduced memory dysfunction and neuronal injury caused by permanent global ischemia in rats. Pharmacol Biochem Behav 2005;82:67-73.
200. Shang YZ, Miao H, Cheng JJ, Qi JM. Effects of amelioration of total flavonoids from stems and leaves of *Scutellaria baicalensis* Georgi on cognitive deficits, neuronal damage and free radicals disorder induced by cerebral ischemia in rats. Biol Pharm Bull 2006;29:805-10.
201. Sharma S, Ying Z, Gomez-Pinilla F. A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. Exp Neurol 2010;226:191-9.
202. Sharma S, Zhuang Y, Ying Z, Wu A, Gomez-Pinilla F. Dietary curcumin supplementation counteracts reduction in levels of molecules involved in energy homeostasis after brain trauma. Neuroscience 2009;161:1037-44.
203. Shukla PK, Khanna VK, Ali MM, Khan MY, Srimal RC. Anti-ischemic effect of curcumin in rat brain. Neurochem Res 2008;33:1036-43.
204. Signoretti S, Di Pietro V, Vagnozzi R, Lazzarino G, Amorini AM, Belli A, *et al*. Transient alterations of creatine, creatine phosphate, N-acetylaspartate and high-energy phosphates after mild traumatic brain injury in the rat. Mol Cell Biochem 2010;333:269-77.
205. Singleton RH, Yan HQ, Fellows-Mayle W, Dixon CE. Resveratrol attenuates behavioral impairments and reduces cortical and hippocampal loss in a rat controlled cortical impact model of traumatic brain injury. J Neurotrauma 2010;27:1091-9.
206. Sinha K, Chaudhary G, Gupta YK. Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. Life Sci 2002;71:655-65.
207. Son D, Lee P, Lee J, Kim H, Kim SY. Neuroprotective effect of wogonin in hippocampal slice culture exposed to oxygen and glucose deprivation. Eur J Pharmacol 2004;493:99-102.
208. Songur A, Sarsilmaz M, Sogut S, Ozyurt B, Ozyurt H, Zararsiz I, *et al*. Hypothalamic superoxide dismutase, xanthine oxidase, nitric oxide, and malondialdehyde in rats fed with fish omega-3 fatty acids. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:693-8.
209. Sonmez U, Sonmez A, Erbil G, Tekmen I, Baykara B. Neuroprotective effects of resveratrol against traumatic brain injury in immature rats. Neurosci Lett 2007;420:133-7.
210. Spain A, Daumas S, Lifshitz J, Rhodes J, Andrews PJ, Horsburgh K, *et al*. Mild fluid percussion injury in mice produces evolving selective axonal pathology and cognitive deficits relevant to human brain injury. J Neurotrauma 2010;27:1429-38.
211. Spector R, Johanson CE. Vitamin transport and homeostasis in mammalian brain: Focus on Vitamins B and E. J Neurochem 2007;103:425-38.
212. Suganuma M, Okabe S, Oniyama M, Tada Y, Ito H, Fujiki H. Wide distribution of [3H](-)-epigallocatechin gallate, a cancer preventive tea polyphenol, in mouse tissue. Carcinogenesis 1998;19:1771-6.
213. Suk K, Lee H, Kang SS, Cho GJ, Choi WS. Flavonoid baicalein attenuates activation-induced cell death of brain microglia. J Pharmacol Exp Ther 2003;305:638-45.
214. Sullivan PG, Geiger JD, Mattson MP, Scheff SW. Dietary supplement creatine protects against traumatic brain injury. Ann Neurol 2000;48:723-9.
215. Sung S, Yao Y, Uryu K, Yang H, Lee VM, Trojanowski JQ, *et al*. Early vitamin E supplementation in young but not aged mice reduces Abeta levels and amyloid deposition in a transgenic model of Alzheimer's disease. FASEB J 2004;18:323-5.
216. Tan EK, Tan C, Fook-Chong SM, Lum SY, Chai A, Chung H, *et al*. Dose-dependent protective effect of coffee, tea, and smoking in Parkinson's disease: A study in ethnic Chinese. J Neurol Sci 2003;216:163-7.
217. Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, *et al*. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: Subanalysis of the JELIS trial. Stroke 2008;39:2052-8.
218. Tang C, Xue H, Bai C, Fu R, Wu A. The effects of Tanshinone IIA on blood-brain barrier and brain edema after transient middle cerebral artery occlusion in rats. Phytomedicine 2010;17:1145-9.

219. Tang C, Xue HL, Bai CL, Fu R. Regulation of adhesion molecules expression in TNF-alpha-stimulated brain microvascular endothelial cells by tanshinone IIA: Involvement of NF-kappaB and ROS generation. Phytother Res 2011;25:376-80.
220. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002;112:659-62.
221. Thiyagarajan M, Sharma SS. Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats. Life Sci 2004;74:969-85.
222. Travis MA, Hall ED. The effects of chronic two-fold dietary vitamin E supplementation on subarachnoid hemorrhage-induced brain hypoperfusion. Brain Res 1987;418:366-70.
223. Usoro OB, Mousa SA. Vitamin E forms in Alzheimer's disease: A review of controversial and clinical experiences. Crit Rev Food Sci Nutr 2010;50:414-9.
224. Varma MR, Dixon CE, Jackson EK, Peters GW, Melick JA, Griffith RP, *et al*. Administration of adenosine receptor agonists or antagonists after controlled cortical impact in mice: Effects on function and histopathology. Brain Res 2002;951:191-201.
225. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL, Xiong Y, Lee CP. Mitochondrial dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111). Neurol Res 1997;19:334-9.
226. Wakade C, King MD, Laird MD, Alleyne CH Jr, Dhandapani KM. Curcumin attenuates vascular inflammation and cerebral vasospasm after subarachnoid hemorrhage in mice. Antioxid Redox Signal 2009;11:35-45.
227. Wang W, Zheng LL, Wang F, Hu ZL, Wu WN, Gu J, *et al*. Tanshinone IIA attenuates neuronal damage and the impairment of long-term potentiation induced by hydrogen peroxide. J Ethnopharmacol 2011;134:147-55.
228. Wang X, Zhao X, Mao ZY, Wang XM, Liu ZL. Neuroprotective effect of docosahexaenoic acid on glutamate-induced cytotoxicity in rat hippocampal cultures. Neuroreport 2003;14:2457-61.
229. Wang XJ, Wang ZB, Xu JX. Effect of salvianic acid A on lipid peroxidation and membrane permeability in mitochondria. J Ethnopharmacol 2005;97:441-5.
230. Wang XJ, Xu JX. Salvianic acid A protects human neuroblastoma SH-SY5Y cells against MPP+-induced cytotoxicity. Neurosci Res 2005;51:129-38.
231. Wang Y, Liu J, Zhang Z, Bi P, Qi Z, Zhang C. Anti-neuroinflammation effect of ginsenoside Rbl in a rat model of Alzheimer disease. Neurosci Lett 2011;487:70-2.
232. Washington CB, Jackson EK, Janesko KL, Vagni VA, Lefferis Z, Jenkins LW, *et al*. Chronic caffeine administration reduces hippocampal neuronal cell death after experimental traumatic brain injury in mice. J Neurotrauma 2005;22:366-70.
233. Wei IH, Tu HC, Huang CC, Tsai MH, Tseng CY, Shieh JY. (-)-Epigallocatechin gallate attenuates NADPH-d/nNOS expression in motor neurons of rats following peripheral nerve injury. BMC Neurosci 2011;12:52.
234. Witham MD, Dove FJ, Sugden JA, Doney AS, Struthers AD. The effect of vitamin D replacement on markers of vascular health in stroke patients - A randomised controlled trial. Nutr Metab Cardiovasc Dis 2010 [In press].
235. Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, Goldstein FC, *et al*. ProTECT: A randomized clinical trial of progesterone for acute traumatic brain injury. Ann Emerg Med 2007;49:391-402, 402.e1-2.
236. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol 2006;197:309-17.
237. Wu A, Ying Z, Gomez-Pinilla F. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma 2004;21:1457-67.
238. Wu A, Ying Z, Gomez-Pinilla F. Omega-3 fatty acids supplementation restores mechanisms that maintain brain homeostasis in traumatic brain injury. J Neurotrauma 2007;24:1587-95.
239. Wu A, Ying Z, Schubert D, Gomez-Pinilla F. Brain and spinal cord interaction: A dietary curcumin derivative counteracts locomotor and cognitive deficits after brain trauma. Neurorehabil Neural Repair 2011;25:332-42.
240. Wu A, 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;24:290-8.
241. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev 2000;80:1107-213.
242. Xiao G, Wei J, Yan W, Wang W, Lu Z. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: A randomized controlled trial. Crit Care 2008;12:R61.
243. Xiong Y, Gu Q, Peterson PL, Muizelaar JP, Lee CP. Mitochondrial dysfunction and calcium perturbation induced by traumatic brain injury. J Neurotrauma 1997;14:23-34.
244. Xu G, Zhao W, Zhou Z, Zhang R, Zhu W, Liu X. Danshen extracts decrease blood C reactive protein and prevent ischemic stroke recurrence: A controlled pilot study. Phytother Res 2009;23:1721-5.
245. Xu K, Xu YH, Chen JF, Schwarzschild MA. Caffeine's neuroprotection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity shows no tolerance to chronic caffeine administration in mice. Neurosci Lett 2002;322:13-6.
246. Xue X, Qu XJ, Yang Y, Sheng XH, Cheng F, Jiang EN, *et al*. Baicalin attenuates focal cerebral ischemic reperfusion injury through inhibition of nuclear factor kappaB p65 activation. Biochem Biophys Res Commun 2010;403:398-404.
247. Yang C, Zhang X, Fan H, Liu Y. Curcumin upregulates transcription factor Nrf2, HO-1 expression and protects rat brains against focal ischemia. Brain Res 2009;1282:133-41.
248. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, *et al*. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid *in vivo*. J Biol Chem 2005;280:5892-901.
249. Yang YB, Piao YJ. Effects of resveratrol on secondary damages after acute spinal cord injury in rats. Acta Pharmacol Sin 2003;24:703-10.
250. Ye R, Kong X, Yang Q, Zhang Y, Han J, Li P, *et al*. Ginsenoside Rd in experimental stroke: Superior neuroprotective efficacy with a wide therapeutic window. Neurotherapeutics 2011;8:515-25.
251. Ye R, Kong X, Yang Q, Zhang Y, Han J, Zhao G. Ginsenoside Rd attenuates redox imbalance and improves stroke outcome after focal cerebral ischemia in aged mice. Neuropharmacology 2011;61:815-24.
252. Ye R, Zhang X, Kong X, Han J, Yang Q, Zhang Y, *et al*. Ginsenoside Rd attenuates mitochondrial dysfunction and sequential apoptosis after transient focal ischemia. Neuroscience 2011;178:169-80.
253. Yoneda H, Shirao S, Kurokawa T, Fujisawa H, Kato S, Suzuki M. Does eicosapentaenoic acid (EPA) inhibit cerebral vasospasm in patients after aneurysmal subarachnoid hemorrhage? Acta Neurol Scand 2008;118:54-9.
254. Yu J, Jia Y, Guo Y, Chang G, Duan W, Sun M, *et al*. Epigallocatechin-3-gallate protects motor neurons and regulates glutamate level. FEBS Lett 2010;584:2921-5.
255. Yuen AW, Sander JW, Fluegel D, Patsalos PN, Bell GS, Johnson T, *et al*. Omega-3 fatty acid supplementation in patients with chronic epilepsy: A randomized trial. Epilepsy Behav 2005;7:253-8.
256. Yune TY, Lee JY, Cui CM, Kim HC, Oh TH. Neuroprotective effect of *Scutellaria baicalensis* on spinal cord injury in rats. J Neurochem 2009;110:1276-87.
257. Zhang WJ, Feng J, Zhou R, Ye LY, Liu HL, Peng L, *et al*. Tanshinone IIA protects the human blood-brain barrier model from leukocyte-associated hypoxia-reoxygenation injury. Eur J Pharmacol 2010;648:146-52.
258. Zhao HF, Li Q, Li Y. Long-term ginsenoside administration prevents memory loss in aged female C57BL/6J mice by modulating the redox status and up-regulating the plasticity-related proteins in hippocampus. Neuroscience 2011;183:189-202.
259. Zhao J, Yu S, Zheng W, Feng G, Luo G, Wang L, *et al*. Curcumin improves outcomes and attenuates focal cerebral ischemic injury via antiapoptotic mechanisms in rats. Neurochem Res 2010;35:374-9.
260. Zheng GQ, Cheng W, Wang Y, Wang XM, Zhao SZ, Zhou Y, *et al*. Ginseng total saponins enhance neurogenesis after focal cerebral ischemia. J Ethnopharmacol 2011;133:724-8.

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 a immunoexcitotoxic disorders, with elevations in cytokines, particularly TNF-α, and an increase in calcium-permeable AMPA receptors in the hippocampus and cortex. This has been demonstrated specifically in the case of seizures.[263,265] 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).[264] 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.[261]

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.[262] 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.

REFERENCES

261. Blaylock RL, Maroon J. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy—A unifying hypothesis. Surg Neurol Int 2011;2:107.
262. Farooqui AA. Potential therapeutic strategies for neurodegenerative diseases. In: Farooqui AA, editor. Neurochemical Aspects of Neurotraumatic and Neurodegenerative Diseases. NY: Springer; 2010. p. 325-82.
263. Grooms SY, Opitz T, Bennett MV, Zukin RS. Status epilepticus decreases glutamate receptor 2 mRNA and protein expression in hippocampal pyramidal cells before neuronal death. Proc Natl Acad Sci U S A 2000;97:3631-6.
264. Jang YJ, Kim J, Shim J, Kim J, Byun S, Oak MH, *et al*. Kaempferol attenuates 4-hydroxynonenal-induced apoptosis in PC12 cells by directly inhibiting NADPH oxidase. J Pharmacol Exp Ther 2011;337:747-54.
265. Vincent P, Mulle C. Kainate receptors in epilepsy and excitotoxicity. Neuroscience 2009;158:309-23.

Russell L. Blaylock
Visiting Professor Biology, Belhaven University,
Theoretical Neurosciences Research,
E-mail: russell.blaylock@gmail.com

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).[266]

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.[267] Many laboratories are searching for pharmacologic agents that may be neuroprotective and neurotherapeutic following traumatic brain injury.[268] 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 kB, 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, minocyline, is also a potent microglial suppressant found to be neuroprotective in both spinal and cerebral trauma.[269] Another anti-inflammatory weapon is hyperbaric oxygen.[267] 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, minocyline and additionally vitamin D_3 , 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.

REFERENCES

266. Blaylock RL, Maroon JC. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy--A unifying hypothesis. Surg Neurol Int 2011;2:107.
267. Harch PG, McCullough V. The oxygen revolution—Hypobaric oxygen therapy. Hatherleigh Press; 2010.
268. Klein AM, Ferrante R. The neuroprotective role of creatine. Subcell Biochem 2007;46:205-43.
269. Kwon BK, Kasa S, Hurlbert JR, Young WV. Inflammatory and structural biomarkers in acute traumatic spinal cord injury. Clin Chem Lab Med 2011;49:425-33.
270. Mills JD, Bailes JE, Sedney CL, Hutchins H, Sears B. Omega-3 fatty acid supplementation and reduction of traumatic axonal injury in a rodent head injury model. J Neurosurg 2011;114:77-84.

Joseph C. Maroon
Department of Neurosurgery, Heindl Scholar in Neuroscience,
University of Pittsburgh Medical Center,
Team Neurosurgeon, The Pittsburgh Steelers
E-mail: maroonjc@upmc.edu