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Combination of micronutrient mixture, probiotics, collagen peptides, omega 3, cannabidiol, and diet may reduce the risk of development and progression of Post-Traumatic Stress Disorder (PTSD), and improve its treatment

Abstract

Post-Traumatic Stress Disorder (PTSD) is a complex psychiatric disorder caused by sudden exposure to a single or repeated traumatic events. The major symptoms include flashbacks, nightmares, hyperarousal, depression, substance abuse, suicidal tendencies, impaired learning ability, and cognitive dysfunction. In 2023, the prevalence of PTSD was 6.8% among civilian, while it was 7% among veterans. In 2018, total national cost for the treatment of PTSD patients was $232.2 billion. Poor diet and lifestyle and enhanced exposure to environmental toxins aggravate the symptoms. Internal stressors causing PTSD include increased oxidative stress, chronic inflammation, intestinal dysbiosis, loss of collagen, dysfunctional omega 3, and excessive release of glutamate. Proposed preventive recommendations include consuming healthy diet and lifestyle, reducing excessive consumption of fat, sugar, alcohol, and caffeine, increasing social interaction, and physical and mental exercises, reducing exposure to environmental toxins. In addition, supplementation with a micronutrient mixture for reducing oxidative stress and chronic inflammation, probiotics with prebiotics for reversing the harmful effects of intestinal dysbiosis, collagen peptides for restoring the loss of collagen, omega 3 for replacing dysfunctional oxidized omega 3, and CBD to improve the levels of serotonin and dopamine, reduce the release of glutamate. The current treatments of PTSD focus on the symptoms of the diseases and not its causes. Psychotherapies are considered gold standard for PTSD treatment, but they produce serious adverse side-effects. Medications include selective serotonin reuptake inhibitors for reducing anxiety and depression, Prazosin for improving PTSD-related sleep disturbance. These drugs cause adverse side-effects. Combining current therapies with the proposed prevention plan would markedly improve the symptoms of PTSD and reduce the progression of this disease.

Keywords: Oxidative stress; Chronic inflammation; PTSD; Prevention; Improved treatment.

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Introduction

Post-Traumatic Stress Disorder (PTSD) is a complex mental disease exhibiting psychiatric disorders that can happen after exposure to a single or repeated traumatic events. The symptoms of PTSD include unwanted reexperiencing of traumatic events (flashbacks, nightmares, and triggered emotional responses), passive and active avoidance of discussions of the traumatic events, hyperarousal, psychiatric disorders including depression, anxiety, substance abuse, suicidal tendencies, impaired learning ability, and cognitive dysfunction [1-3]. These symptoms may lead to impairment of the ability to function in social or family life and can lead to marital stress, and occupational instability. Some PTSD symptoms overlap with other diseases including chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities [1].

External and internal stressors are major contributors to the initiation and progression of PTSD. Any effective prevention and improved treatment plan must attenuate both stressors.

There is no effective preventive strategy for PTSD because many external stressors which induce PTSD are beyond any one control; however, an effective preventive strategy can be implemented in troops being sent to combat zones. In most cases, the symptoms of PTSD appear within 3 months after the exposure to traumatic events, but in some cases, it might take a year or more. Thus, an effective proposed preventive plan can be implemented among civilian or troops soon after exposure to traumatic events.

The current treatments for PTSD focus on improving the symptoms of the disease, and not its causes. They improve some symptoms of PTSD but produce adverse side effects. Combining current treatments with the proposed prevention plan to attenuate causes of PTSD by natural products may markedly improve effectiveness of therapies and reduce the progression of the disease.

This review briefly describes prevalence, cost, symptoms, neuropathology of the brain, external and internal stressors that participate in the development and progression of PTSD. It also proposes novel plans for prevention and improved treatment of PTSD by using natural products.

Prevalence of PSTD in the USA

The prevalence of PTSD in adult population depends upon gender, age, and war zone. In 2023, 3.6% of adults had PTSD. Females were more sensitive than males. 5.2% females had PTSD, whereas only 1.8% of males had PTSD. Lifetime prevalence of PTSD was 6.8%. Serious impairment of PTSD symptoms was observed among 36.6% of cases, 33.1% showed moderate and 30.2% revealed mild level.

In 2023, individuals aged 18-29 years had 4%, aged 30-44 years had 3.5%, aged 40-60 year had 5.3%, and aged 60 years and over had 1.0% PTSD (Data are taken from The NIH National Institute of Mental Health, 2024).

Among veterans, lifetime prevalence of PTSD was 7%. Females were more sensitive than males in developing symptoms. It is evident by the data which show that 13% of females developed PTSD symptoms, whereas only 6% of men acquired such symptoms. In 2023, 11% of females had PTSD, whereas only 5% of males developed it. The prevalence of PTSD among Veterans aged 18-29 years was 15%, it was 10% among aged 30-44 years, it was 9% among aged 45-64 years, and it was only 4% among aged 65 years. The prevalence of PTSD among veterans depends on the length of stay in war zone. For example, among Vietnam veterans, lifetime prevalence was 15% in females and 17% in men. The data were taken from the US Department of Veterans Affairs, Vietnam veterans 2024).

Cost of treatment of PTSD

In 2018, total cost treatment of PTSD patients was $232.2 billion ($19, 630 per individual). It was $189.5 billion for civilian with PTSD ($18,640 per individual) and $42.7 billion for military population with PTSD ($25,684 per military personal) [4].

Symptoms of PTSD

The symptoms of PTSD often appear within 3 months of the exposure to traumatic stressors, and they include unwanted reexperiencing of the trauma in memory (flashbacks, nightmares, triggered emotional responses), passive and active avoidance (emotional numbing, avoidance of discussions about the traumatic event), and hyperarousal [5,6]. In addition, PTSD is usually accompanied by other psychiatric and medical comorbidities, including depression, substance abuse, cognitive dysfunction, and other problems of physical and mental health [7,8]. These problems may lead to impairment of the ability to function in social or family life, including occupational instability, marital stress and family problems. Some of the symptoms of PTSD overlap with other diseases including chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities [9]. The severity in Obstructive Sleep Apnea (OSA) was directly related to suicidal tendency in PTSD patients. Depression was considered a mediator of the association between Respiratory Disturbance Index (RDI) and suicidal tendency [10].

Brain pathology associated with PTSD symptoms

The neuropathology of PTSD patients is not well defined, possibly due to the lack of sufficient autopsied brain tissues. MRI (magnetic resonance imaging) of the brain of PTSD patients revealed the following changes: (a) reduced volume of the hippocampus [11-13] which may account for cognitive dysfunction. Alcohol consumption accelerates reduction in the hippocampus volume in PTSD patients [14], (b) Reduced cerebellar volume was associated with mood changes, depression, and anxiety in patients with PTSD, whereas reduction in volume of the vermis was associated with an early traumatic life experience which may be considered a risk factor for future development of PTSD [15], (c) accelerated brain atrophy in the brain stem, frontal and temporal lobes was associated with increased severity of the PTSD symptoms [16]. In addition, it was observed that greater rates of brain atrophy were associated with greater rates of decline in verbal memory and delayed facial recognition. The atrophy of the frontal and limbic cortices was associated with the severity of the PTSD symptom, and (d) reduced gray matter volume in the left anterior cingulate cortex was associated with the development of PTSD, whereas reduction of gray matter volume in the right pulvinar and left pallidus was associated with severe trauma without PTSD [17]. MRI study on the brains of twins revealed that significant reduction in gray matter volume occurred in four brain regions: right hippocampus, pregenual anterior cingulate cortex, and left and right insulae in twins with PTSD compared to that in twins without PTSD [18]. A review of 9 studies revealed that reduction in gray matter in the anterior cingulate cortex, ventromedial prefrontal cortex, left temporal pole/middle temporal gyrus, and left hippocampus occurred in PTSD patients compared to individuals exposed to trauma with-

out PTSD [19]. Furthermore,

(a) Reduction in volume of Anterior Cingulate Cortex, which is involved in cognitive, emotional, and autonomic functions, contributes to the development of PTSD [20] and in volume of cerebellum which is involved in fear perception, anticipation, and recollection, mood change, anxiety, and other PTSD symptoms, whereas reduction in volume of the vermis was associated with an early traumatic life experience, and may be considered a risk factor for future development of PTSD [15]. Decreased volume of the left amygdala, right amygdala, and left hippocampus was present in PTSD patients compared to trauma-exposed individuals without PTSD; however, the volume of right hippocampus was not reduced in patients with PTSD [21].

(b) Reduction in volume of the middle temporal and inferior occipital cortices was associated with greater re-experiencing score, whereas reduced volume of the insula/parietal operculum and inferior temporal gyrus predicted flashback symptoms in patients with PTSD [22,23].

External stressors causing PTSD

External stressors which cause PTSD include exposure to sudden or repeated traumatic events, such as war, terrorism, natural or human-caused disaster. In addition, individuals who experience a violent personal assault, such as rape, mugging, domestic violence, sudden death of a family member, accidents, and sustained mild traumatic brain injury [24,25]. There is also a strong direct relationship between mild Traumatic Brain Injury (TBI) and PTSD [24,25]. Approximately, 17.6 percent PTSD can develop from mild to severe TBI [26]. External stressors which aggravate PTSD symptoms include poor diet, and lifestyle [27]. Exposure to poor environment also can aggravate the symptoms of mental health associated with PTSD [28].

Internal stressors causing PTSD

Increased oxidative stress

One of the earliest internal stressors induced by the external stressors is increased oxidative stress in PTSD because excess free radicals generated by external stressors overtakes antioxidant system against free radicals causing increased oxidative stress. Evidence for the involvement of increased oxidative stress in PISD is presents here.

Human studies

One of earliest internal stressors induced by external stressors is increased oxidative stress which participates in the development and progression of PTSD including psychiatric disorders [29]. Stress evokes a sustained increase in Nitric Oxide Synthase (NOS) activity that can generate excessive amounts of nitric oxide [30,31]. Oxidation of nitric oxide produces preroxynitrite, which is very toxic to nerve cells [32], Platelet monoamine oxidase, which generates excessive amounts of free radicals while degrading catecholamines, is also elevated in patients with PTSD [33]. This is further confirmed by the fact that depletion of catecholamines has been observed in patients with PTSD [34]. The levels of serum Paraoxonase-1 (PON-1) enzyme activity were lower and those of Malondialdehyde (MDA) were higher in PTSD patients who survived an earthquake compared to those earthquake survivors who did not develop this disease. This study suggests that increased oxidative stress is associated with the development of PTSD [23].

Animal studies

The levels of Reactive Oxygen Species (ROS) and proinflammatory cytokines were increased in an animal model of PTSD. Treatment with valproic acid, an inhibitor of histone deacetylase, normalized these biochemical defects, decreased anxiety, and restored the levels of neurotransmitters such as catecholamines and serotonin [35]. In rat model of PTSD, the levels of oxidative stress and inflammatory cytokines were elevated in the brain (hippocampus, amygdala, and prefrontal cortex), adrenal glands, and whole blood, suggesting that damage to multiple organs were involved in the progression of PTSD [36]. Exposure to enriched environment reversed behavioral impairments (anxiety-like behavior, enhanced fear learning behavior, and spatial memory deficits) by reducing oxidative stress in the hippocampus and pre-frontal cortex [37]. Treatment with apocynin, a methoxy-substituted catechol, an inhibitor of NOX2 (nicotinamide adenosine dinucleotide phosphate NADPH-2) that produces free radicals, reduced the levels of markers of oxidative stress (malondialdehyde, NOX2, and 4-hydroxynonenal) and proinflammatory cytokine IL-6 in the hippocampus of rat model of PTSD [38]. Both human and animal investigations suggest that attenuation of oxidative stress appears to be one of the rational choices for reducing the risk of onset and progression of PTSD.

Chronic inflammation in PTSD

If oxidative damage to cells is not fully repaired, chronic inflammation sets in motion. Increased oxidative stress also produces chronic inflammation in the brain by activating microglia. The levels of markers of chronic inflammation such as Interleukin-6 (IL-6) [39], and IL-6 receptors [40], Tumor Necrosis Factor-alpha (TNF-alpha) and IL-1beta were elevated in patients with PTSD in comparison to control subjects [41]. The levels of CRP and IL-6 receptors were elevated in patients with PTSD [42]. Increased levels of chronic inflammation may also contribute to the cognitive dysfunctions commonly observed in patients with PTSD. Elevated levels of neuroinflammation were repeatedly observed in patients with PTSD [43,44]. Activated glia that release proinflammatory cytokines are found in patients with PTSD [39,40]. The prevalence of chronic pain is high among patients with PTSD.

Other internal stressors contributing to PTSD

In addition to increased oxidative stress and chronic inflammation, other internal stressors such as intestinal dysbiosis, loss of collagen, dysfunctional omega 3, and reduced levels of serotonin and dopamine in neurons, and increased glutamate release and deceased release of Gamma-Aminobutyric Acid (GABA) participate in the initiation and progression of PTSD. They are briefly described here.

Intestinal dysbiosis in PTSD

Intestinal dysbiosis refers to increase in the number of harmful bacteria and decline in the number of beneficial bacteria in the gut. It is one of the interna stressors which contributes to the development and progression of PTSD by enhancing the levels of markers of chronic inflammation [45]. Several review articles have concluded that there is a direct link between intestinal dysbiosis and PTSD [46]. The patients with PTSD show enhanced inflammation and markers of proinflammatory cytokines [47] which could have happened because of existence of intestinal dysbiosis. Therefore, supplementation with probiotics with prebiotics may slow down the rate of progression of

PTSD symptoms by reversing the harmful effects of intestinal dysbiosis.

Loss of collagen in PTSD

Collagen represents approximately 30 % of total body proteins is present in all organs. There are 28 different types of collagens. One of the major functions of collagen is to maintain structural and functional integrity of all organs. Any alteration in the structure of the brain could alter its fucntion. This was demonstrated in a clinical study in which 26 men and 4 women aged 49-63 years (mean age 56.1+/- 3.6 years) were recruited. They received 5 g of collagen hydrolysate for 4 weeks. The structure of the brain was determined by MRI and function of the brain was determined by known techniques. The results showed that oral consumption of collagen hydrolysate for 4 weeks improved the structure of the brain as well as cognitive language ability [48]. Several studies have reported that the ingestion of Collagen Hydrolysate (CH) helps brain to recover from injury by promoting angiogenesis [49]. CH also acts as a neuroprotective action by suppressing inflammatory effects [50]. It promoted learning and memory in aged mice [50]. PTSD is associated with loss of bone mass, altered structure and impaired mechanical strength [51]; therefore, supplementation with collagen peptide may improve bone structure. These studies suggest that supplementation with collagen peptides may improve brain structure and function in PTSD patients.

Loss of omega 3 function in PTSD

Omega 3 is an essential fatty acid which is not made in our body. The diet remains the only source of omega 3. It is essential for our growth and survival. Omega3 includes DHA, EPA, and ALA. DHA and EPA come from fish diet, whereas ALA come from nuts such as flax seed. Omega-3 fatty acids, particularly DHA, may play a role in preventing or reducing PTSD symptoms. In the single-prolonged stress induced rat model of PTSD, both short- and long-term memory were impaired. Omega 3 is easily oxidized in an internal high oxidative environment of PTSD patients and become dysfunctional Treatment with omega 3 prevented this impairment, possibly through normalizing antioxidant mechanisms in the hippocampus [52]. Fifteen Patients were admitted to ICU at the Japanese hospital immediately after accidental injury. They were given omega 3 daily for 12 weeks. Results showed that omega 3 supplementation reduced some symptoms of PTSD. Omega 3 treatment enhances the serum level of BDNF which induces hippocampal neurogenesis that reduces the development of fear and anxiety [53]. In addition, omega 3 rich fish oil can facilitate fear-extinction learning by facilitating hippocampal neurogenesis [54-56]. Omega-3 maintains endocannabinoid-mediated neuronal functions [57] that facilitates extinction of fear memories. Such actions against fear memory are like those of beta-blockers [58] which are FDA approved drug. Omega 3 rich fish oil can reduce sympathetic nerve activity [59,60] that possibly plays an important role in the development of PTSD [61]. Thus, supplementation with omega 3 would be useful in both prevention and improved management of PTSD symptoms. Simultaneous attenuation of above internal stressors by natural products would be very effective in prevention as well as improved current treatment of PTSD.

Reduced level of serotonin in PTSD

Serotonin transporter (5-HTT) located in the amygdala regulates stress response. Therefore, deficient 5-HTT function and abnormal amygdala activity may contribute to the development of PTSD. This was shown by the fact that PTSD patients exhibited reduced amygdala expression of 5-HTT, as measured by PET (positron emission tomography) using a radioactive tracer of 5-HTT (11C-AFM). It was observed that reduced amygdala 5-HTT binding was associated with higher anxiety and depression symptoms in PTSD patients [62]. The level of serotonin in the serum was lower in patients with PTSD than control subjects [63]. Therefore, improving the level of serotonin in the brain would be useful in the prevention and treatment of some symptoms of PTSD.

Dysregulation of dopamine signaling pathway in PTSD

Dysregulation of dopamine signaling pathways alters the brain reward system [64]. Dopamine plays a crucial role in reward functioning of the brain. Stress can impair dopamine reward system [65]. Therefore, improving the level of dopamine in the brain would be useful in the management of some symptoms of PTSD.

Increased release of glutamate and decreased release of Gamma-Aminobutyric Acid (GABA) in PTSD

Several studies suggest that the imbalances between activities of glutamatergic and GABAnergic neurons contribute to the severity of the symptoms of PTSD including fear and anxiety. The glutamatergic systems appear to play an important role in the pathophysiology of PTSD [66]. Stress-induced glutamate release and glucocorticoids have been implicated to cause hippocampal atrophy in patients with PTSD. This observation is not unexpected because glutamate in high doses is known to be neurotoxic. Glutamate and Nitric Oxide (NO) released during stress play a central role in maintaining anxiety disorders [30,66-68]. Stress activates glutamate-NMDA receptors and decreases brain-derived neurotrophic factors, and excessive amounts of glutamate can cause death to cholinergic neurons that may account for the cognitive dysfunction associated with PTSD. The levels of glutamate in the serum of patients with established PTSD or partial PTSD were higher compared to those without PTSD. In addition, higher serum levels of glutamate were associated with the severity of PTSD and major depressive disorder [68]. This study also revealed that the glutamine/glutamate ratio was inversely associated with the severity of PTSD but not with the severity of major depressive disorder. Dysfunction of glutamate neurotransmission appears to be the main feature of stress-related psychiatric disorders including PTSD, anxiety, and mood changes [69]. Glutamate induced the release of CRF (corticotropin-releasing factor) may account for the atrophy of hippocampus [66]. The role CRF-mediated biochemical events in the pathogenesis of PTSD are further supported by the observation that patients with PTSD had increased levels of CRF [70]. Stress released excessive amounts of glutamate and nitric oxide and they play an important role in maintaining anxiety disorders. Stress also activated glutamate-NMDA receptors and reduce the levels of BDNF (brain-derived neurotrophic factor) that contributed to the death of cholinergic neurons. This may account for the cognitive dysfunction in patients with PTSD symptoms.

Using in vivo proton magnetic resonance spectroscopy (1H MRS), it was found that the levels of GABA were lower and the levels of glutamate were higher in the parieto-occipital and temporal cortices of PTSD patients compared to those who were exposed to trauma but had not developed PTSD symptoms [71]. This study also demonstrated that increased anxi-

ety symptoms scores and Insomnia Severity Index (ISI) scores commonly found in PTSD were associated with the lower levels of GABA and higher levels of glutamate. Imbalances between glutamate and GABA contribute to the apoptosis in the hippocampus of animal model of PTSD [72]. Therefore, blocking the release of glutamate and reducing the toxicity of glutamate as well as increasing the release of GABA would be useful in reducing the risk and progression of PTSD.

Effects of antioxidants on reducing oxidative stress and chronic inflammation in PTSD

Despite strong evidence for the involvement of increased oxidative stress and inflammation in the initiation and progression of PTSD, only a few studies with individual antioxidants have been conducted in animal models of PTSD. They are described here.

Curcumin

Curcumin exhibits strong antioxidant and anti-inflammatory, provides neurotrophic protection, alleviates the mental disorders and anxiety-like behaviors of PTSD [73]. Curcumin also reduces anxiety and fear extinction learning in rats' model of PTSD during developmental stages [74]. It has been reported that low-dose curcumin alleviates stress disorders, whereas high-dose curcumin reduces hippocampal neuroinflammation to prevent PTSD-like behavior.

Resveratrol

Resveratrol is an effective agent for the treatment of depression, anxiety and PTSD in mice [75]. It exhibits antioxidant and anti-inflammatory effects. Resveratrol ameliorates anxiety-like behaviors and fear memory deficits in a rat model of post-traumatic stress disorder [76].

Vitamin C and Vitamin E

Vitamin C [77] and Vitamin E [78] prevented memory loss in rat model of PTSD.

A mixture of antioxidants

Vascular dysfunction is associated with PTSD in young adults. Supplementation with a mixture of antioxidants containing Vitamin C, Vitamin E, and alpha-lipoic acid restored vascular dysfunction to normal level [79].

Although a few studies with individual antioxidants have been performed on animal models of PTSD, no such study has been performed in human PTSD. Since investigations with individual antioxidants in other neurodegenerative diseases produced no effect, although animal studies showed consistent benefits [80]. It is likely that use of single antioxidants would produce no significant benefit in prevention or improving the symptoms of human PTSD. Some potential causes include:

(a) antioxidants show differential subcellular distribution and different mechanisms of action therefore; a single antioxidant cannot protect all parts of the cell; (b) a single antioxidant in a high internal oxidative environment of PTSD patients would be oxidized and can then itself acts as a prooxidant rather than as an antioxidant; (c) Elevated levels of antioxidant enzymes and dietary and endogenous antioxidant compounds are needed to reduce oxidative stress and chronic inflammation; a single antioxidant cannot achieve this goal.

To avoid problems associated with the use of individual antioxidants in reducing oxidative stress and inflammation, We have proposed that in order to simultaneously reduce oxidative stress and chronic inflammation, it is essential to elevate both antioxidant enzymes and multiple antioxidant compounds [81]. The levels of multiple antioxidants can easily be elevated by an oral supplementation but increasing the levels of antioxidants require activation of a nuclear transcriptional factor Nrf2. Therefore, it is essential to understand the regulation of activation of Nrf2.

Activation of Nrf2 (Nuclear factor-erythroid-2-related factor 2)

Properties of Nrf2

The nuclear transcriptional factor, Nrf2 belongs to the Cap 'n' Collar (CNC) family that contains a conserved basic leucine zipper (bZIP) transcriptional factor [82]. Under physiological condition, Nrf2 is associated with Kelch-like ECH associated protein 1 (Keap1), which acts as an inhibitor of Nrf2 [82]. Keap1 protein serves as an adaptor to link Nrf2 to the ubiquitin ligase CuI-Rbx1 complex for degradation by proteasomes and maintains the steady levels of Nrf2 in the cytoplasm. Nrf2-keap1 complex is primarily located in the cytoplasm; Keap1 acts as a sensor for ROS/electrophilic stress.

Activation of Nrf2 by ROS

During acute oxidative stress, ROS (reactive oxygen species) is needed to activate Nrf2 which then dissociates itself from Keap1- CuI-Rbx1 complex and translocate in the nucleus where it heterodimerizes with a small Maf protein, binds with ARE leading to increased expression of target genes coding for several cytoprotective enzymes including antioxidant enzymes [83,84].

Development of ROS-resistant Nrf2

During chronic oxidative stress, Nrf2 becomes resistant to ROS [85,86], suggesting that activation of Nrf2 by a ROS-independent mechanism exists. This is evidenced by the fact that increased chronic oxidative stress occurs despite the presence of Nrf2 in PTSD. The question arises as to how to activate ROS-resistant Nrf2 in human PTSD.

Certain antioxidants activate ROS-resistant Nrf2

Some examples are vitamin E and genistein [87], alpha-lipoic acid [88], curcumin [89], resveratrol [90], omega-3-fatty acids [91], glutathione [92], NAC [93], and coenzyme Q10 [94].

Binding of Nrf2 with ARE (Antioxidant Response Element) in the nucleus

An activation of Nrf2 alone is not sufficient to increase the levels of antioxidant enzymes. Activated Nrf2 must bind with ARE in the nucleus for increasing the expression of target genes coding for antioxidant enzymes. This binding ability of Nrf2 with ARE was impaired in aged rats and this defect was restored by supplementation with alpha-lipoic acid [88]. It is unknown whether the binding ability of activated Nrf2 with ARE is impaired in PTSD.

Proposed micronutrient mixture for reducing oxidative stress and chronic inflammation

Ingredients

This micronutrient mixture contains vitamin A (retinyl palmi-

tate), Vitamin E (both d- alpha-tocopherol acetate and d-alpha-tocopheryl succinate), natural mixed carotenoids, Vitamin C (calcium ascorbate), vitamin D3, all B-Vitamins, coenzyme Q10, alpha-lipoic acid, N-Acetylcysteine (NAC), resveratrol, curcumin, quercetin, green tea extract, and minerals selenium and zinc. This micronutrient mixture has no iron, copper, manganese, or heavy metals. This mixture has been tested clinically for its effectiveness in reducing oxidative stress and chronic inflammation.

Current prevention plan for PTSD

Currently, there is no effective preventive plan for PTSD. Since exposure to traumatic events occur suddenly, it is difficult to implement any prevention plan. However, an effective preventive strategy can be implemented in troops being sent to combat zones. Since in most cases, the symptoms of PTSD appear within 3 months after the exposure to traumatic events, and in some cases, it might take a year or more, an effective prevention plan can be implemented during this period in both troops and civilian.

Proposed prevention plan for PTSD using natural products

Reducing the effects of external stressors

Proposed prevention recommendations include consuming healthy diet and lifestyle, reducing excessive consumption of fat and sugar, alcohol, and caffeine, increasing social interaction and physical and mental exercises and reduced exposure to environmental toxin including EMF radiation as much as possible.

Reducing the effects of internal stressors

Since increased oxidative stress and chronic inflammation play a central role in the initiation and progression of PTSD, we propose to simultaneously attenuate them by the proposed micronutrient mixture. In addition, we propose to supplement with probiotics with prebiotics which would reverse the harmful effects of intestinal dysbiosis, collagen peptides which would restore the loss of collagen and improve structure and function of the brain, and omega 3 which would replace dysfunctional omega 3. Clinical studies should be initiated to test the validity of the proposed prevention plan to reduce the risk of developing PTSD.

Current treatments of PTSD

Use of psychotherapy

At present, the management of PTSD in the USA emphasizes improving the symptoms of the diseases and not its causes which include internal and external stressors. Department of Defense (DOD) recommends the use of trauma-focused psychotherapies such as Cognitive Processing Therapy (CPT), Prolonged Exposure Therapy (PE), Eye Movement, Desensitization, and Restructuring (EMDR), and others which are considered gold standard for treatment of PTSD symptoms [95]. Adverse side-effects of psychotherapy include emergence of new symptoms, enhancement of existing symptoms, treatment failure, suicidal tendency, occupational problems, and strained relationship [96-98].

Use of medications

Medications are recommended for PTSD patients who have residual symptoms after psychotherapy or are unable or unwilling to access psychotherapy. Medications used in the management of PTSD symptoms include selective serotonin reuptake inhibitors (i.e., fluoxetine, paroxetine, and sertraline) and the serotonin-norepinephrine reuptake inhibitor venlafaxine. Other medications include Prozac and Zoloft for reducing anxiety and depression. Patients with PTSD often have sleep disturbance related to hyperarousal or nightmares. Prazosin is effective for the treatment of PTSD-related sleep disturbance [99,100]. Adverse side-effects include nausea, diarrhea, fatigue, drowsiness, headache, sexual dysfunction, insomnia, and loss of memory. It is not certain whether psychotherapy or medications would reduce the rate of progression of the PTSD.

Proposed plan to improve current treatments of PTSD

Proposed plan to improvement of PTSD includes combining current treatments with proposed prevention plan would improve symptoms of PTSD and reduce the progression of this disease. A clinical study has reported that supplementation with N-Acetylcysteine (NAC) in combination of cognitive behavior therapy improved the symptoms in patients with PTSD and substance use disorder [101].

Cannabidiol (CBD)

It acts as a strong antioxidant and anti-inflammation activities through complex mechanisms [102]. In addition, CBD enhances the levels of serotonin by acting as an inhibitor serotonin-reuptake and stimulates serotonin receptors to form new serotonin which would decreases the symptoms of anxiety depression. It also stimulates dopamine D2 receptors causing increase in dopamine levels which leads to happiness. CBD also decreases the release of glutamate and enhances the release of Gamma-Aminobutyric Acid (GABA) that reduces hyperactivity and enhance calmness.

Conclusion

Post-Traumatic Stress Disorder (PTSD) is a complex psychiatric disorder caused by sudden exposure to a traumatic event among civilian or troops in war zone. External stressors which initiate and promote PTSD include exposure to sudden or repeated traumatic events, such as war, terrorism, natural or human-caused disaster or individuals who experience a violent personal assault, such as rape, mugging, domestic violence, sudden death of a family member, accidents, and sustained mild traumatic brain injury leads to PTSD symptoms. In addition, consuming poor diet and lifestyle and excessive exposure to poor environment including EMF radiation, aggravate the rate of progression and symptoms of PTSD. These symptoms include flashbacks, nightmares, and triggered emotional response, hyperarousal, depression, substance abuse, suicidal tendencies, impaired learning ability, and cognitive dysfunction. In addition to external stressors, internal Stressors which include increased oxidative stress, chronic inflammation, intestinal dysbiosis, loss of collagen, dysfunctional omega 3, and excessive release of glutamate and decreased level of Gamma-Aminobutyric Acid (GABA) contribute to the development and progression of PTSD. The preventive plan for PTSD has not been developed because traumatic events suddenly occur. However, such a plan can be implemented within 3 months of exposure. Proposed preventive recommendations include consuming healthy diet and lifestyle, reducing excessive consumption of fat, sugar, alcohol, and caffeine, increasing social interaction and physical and mental exercises, reducing exposure to environmental toxin including EMF radiation as much as possible. This plan also includes attenuation of internal stressors by a micronutrient mixture which would decrease oxidative stress and chronic

inflammation, probiotics with prebiotics which would reverse the harmful effects of intestinal dysbiosis, collagen peptides which will restore the loss of collagen and improve structure and function of the brain, and omega 3 which will replace dysfunctional oxidized omega 3. Current treatments of PTSD in the USA emphasize improving the symptoms of the diseases and not its causes. Current treatment has focused on using psychotherapies which are considered gold standard for improving the symptoms of PTSD. Adverse side-effects include emergence of new symptoms, enhancement of existing symptoms, treatment failure, suicidal tendency, occupational problems, and strained relationship. Medications include selective serotonin reuptake inhibitors (i.e., fluoxetine, paroxetine, and sertraline) and the serotonin-norepinephrine reuptake inhibitor venlafaxine, and Prozac and Zoloft for reducing anxiety and depression. Prazosin is effective for the treatment of PTSD-related sleep disturbance. Adverse side-effects include nausea, diarrhea, fatigue, drowsiness, headache, sexual dysfunction, insomnia, and loss of memory. It is not certain whether psychotherapy or medications reduce the rate of progression of the PTSD. We propose that combination of current therapies with the suggested prevention plan would improve symptoms of PTSD and reduce the progression of this disease. In addition, supplementation with Cannabidiol (CBD) would enhance the levels of serotonin by acting as an inhibitor serotonin-reuptake and stimulating serotonin receptors causing increased level pf serotonin that decreases the symptoms of anxiety and depression. It also stimulates dopamine D2 receptors causing enhanced level of dopamine which causes happiness. CBD also decreases the release of glutamate and enhances the release of Gamma-Aminobutyric Acid (GABA) that reduces hyperactivity and enhance calmness.

Declarations

Ethical statement: Since it is a review manuscript, ethical statement is not needed. Any ethical statement related to a review paper has been met.

Conflict of interest: The author is Chief Scientific Officer of Engage Global of Utah. This company sells nutritional products to consumers.

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References

1. Stander VA, Merrill LL, Thomsen CJ, Milner JS. Posttraumatic stress symptoms in Navy personnel: prevalence rates among recruits in basic training. J Anxiety Disord. 2007; 21: 860-870.

2. King DL, Weathers FW. Confirmatory factor analysis of the clinician-administered PTSD scale: evidence for the dimensionality of posttraumatic stress disorder. Psychol Assess. 1998; 10: 90-96.

3. Burriss L, Ayers E, Ginsberg J, Powell DA. Learning and memory impairment in PTSD: relationship to depression. Depress Anxiety. 2008; 25: 149-157.

4. Davis LL, Schein J, Cloutier M, Gagnon-Sanschagrin P, Maitland J, Urganus A, et al. The economic burden of posttraumatic stress disorder in the United States from a societal perspective. J Clin Psychiatry. 2022; 83.

5. Baskar R, Balajee AS, Geard CR, Hande MP. Isoform-specific activation of protein kinase C in irradiated human fibroblasts and their bystander cells. Int J Biochem Cell Biol. 2008; 40: 125-134.

6. Leskin GA, Kaloupek DG, Keane TM. Treatment for traumatic memories: review and recommendations. Clin Psychol Rev. 1998; 18: 983-1001.

7. Brewin CR. A cognitive neuroscience account of posttraumatic stress disorder and its treatment. Behav Res Ther. 2001; 39: 373-393.

8. King LA, King DW, Fairbank JA, Keane TM, Adams GA. Resilience-recovery factors in post-traumatic stress disorder among female and male Vietnam veterans: hardiness, postwar social support, and additional stressful life events. J Pers Soc Psychol. 1998; 74: 420-434.

9. Pall ML. Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO/ONOO- cycle. Med Hypotheses. 2007; 69: 821-825.

10. Gupta MA, Sheridan AD. Fear of sleep may be a core symptom of sympathetic activation and the drive for vigilance in posttraumatic stress disorder. J Clin Sleep Med. 2018; 14: 2093.

11. Bremner JD, Scott TM, Delaney RC, Southwick SM, Mason JW, Johnson DR, et al. Deficits in short-term memory in posttraumatic stress disorder. Am J Psychiatry. 1993; 150: 1015-1019.

12. Tischler L, Brand SR, Stavitsky K, Labinsky E, Newmark R, Grossman R, et al. The relationship between hippocampal volume and declarative memory in a population of combat veterans with and without PTSD. Ann N Y Acad Sci. 2006; 1071: 405-409.

13. Villarreal G, Hamilton DA, Petropoulos H, Driscoll I, Rowland LM, Griego JA, et al. Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. Biol Psychiatry. 2002; 52: 119-125.

14. Starcevic A, Dimitrijevic I, Aksic M, Stijak L, Radonjic V, Aleksic D, et al. Brain changes in patients with posttraumatic stress disorder and associated alcoholism: MRI-based study. Psychiatr Danub. 2015; 27: 78-83.

15. Baldacara L, Jackowski AP, Schoedl A, Pupo M, Andreoli SB, Mello MF, et al. Reduced cerebellar left hemisphere and vermal volume in adults with PTSD from a community sample. J Psychiatr Res. 2011; 45: 1627-1633.

16. Cardenas VA, Samuelson K, Lenoci M, Studholme C, Neylan TC, Marmar CR, et al. Changes in brain anatomy during the course of posttraumatic stress disorder. Psychiatry Res. 2011; 193: 93-100.

17. Chen Y, Fu K, Feng C, Tang L, Zhang J, Huan Y, et al. Different regional gray matter loss in recent onset PTSD and non-PTSD after a single prolonged trauma exposure. PLoS One. 2012; 7: e48298.

18. Kasai K, Yamasue H, Gilbertson MW, Shenton ME, Rauch SL, Pitman RK. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol Psychiatry. 2008; 63: 550-556.

19. Kuhn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biol Psychiatry. 2013; 73: 70-74.

20. Meng Y, Qiu C, Zhu H, Lama S, Lui S, Gong Q, et al. Anatomical deficits in adult posttraumatic stress disorder: a meta-analysis of voxel-based morphometry studies. Behav Brain Res. 2014; 270: 307-315.

21. Morey RA, Gold AL, LaBar KS, Beall SK, Brown VM, Haswell CC, et al. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Arch Gen Psychiatry. 2012; 69: 1169-1178.

22. Kroes MC, Whalley MG, Rugg MD, Brewin CR. Association between flashbacks and structural brain abnormalities in posttrau-

matic stress disorder. Eur Psychiatry. 2011; 26: 525-531.

23. Atli A, Bulut M, Bez Y, Kaplan I, Ozdemir PG, Uysal C, et al. Altered lipid peroxidation markers are related to post-traumatic stress disorder (PTSD) and not trauma itself in earthquake survivors. Eur Arch Psychiatry Clin Neurosci. 2016; 266: 329-336.

24. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. N Engl J Med. 2008; 358: 453-463.

25. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. Am J Epidemiol. 2008; 167: 1446-1452.

26. Alway Y, Gould KR, McKay A, Johnston L, Ponsford J. The evolution of post-traumatic stress disorder following moderate-to-severe traumatic brain injury. J Neurotrauma. 2016; 33: 825-831.

27. van den Berk-Clark C, Secrest S, Walls J, Hallberg E, Lustman PJ, Schneider FD, et al. Association between posttraumatic stress disorder and lack of exercise, poor diet, obesity, and co-occurring smoking: a systematic review and meta-analysis. Health Psychol. 2018; 37: 407-416.

28. Tota M, Karska J, Kowalski S, Piatek N, Pszczolowska M, Mazur K, et al. Environmental pollution and extreme weather conditions: insights into the effect on mental health. Front Psychiatry. 2024; 15: 1389051.

29. Bremner JD. Stress and brain atrophy. CNS Neurol Disord Drug Targets. 2006; 5: 503-512.

30. Harvey BH, Bothma T, Nel A, Wegener G, Stein DJ. Involvement of the NMDA receptor, NO-cyclic GMP and nuclear factor kappa-B in an animal model of repeated trauma. Hum Psychopharmacol. 2005; 20: 367-373.

31. Harvey BH, Oosthuizen F, Brand L, Wegener G, Stein DJ. Stress-restress evokes sustained iNOS activity and altered GABA levels and NMDA receptors in rat hippocampus. Psychopharmacology (Berl). 2004; 175: 494-502.

32. Pall ML, Satterlee JD. Elevated nitric oxide/peroxynitrite mechanism for the common etiology of multiple chemical sensitivity, chronic fatigue syndrome, and posttraumatic stress disorder. Ann N Y Acad Sci. 2001; 933: 323-329.

33. Richardson JS. On the functions of monoamine oxidase, the emotions, and adaptation to stress. Int J Neurosci. 1993; 70: 75-84.

34. Pivac N, Knezevic J, Kozaric-Kovacic D, Dezeljin M, Mustapic M, Rak D, et al. Monoamine oxidase (MAO) intron 13 polymorphism and platelet MAO-B activity in combat-related posttraumatic stress disorder. J Affect Disord. 2007; 103: 131-138.

35. Wilson CB, McLaughlin LD, Ebenezer PJ, Nair AR, Francis J. Valproic acid effects in the hippocampus and prefrontal cortex in an animal model of post-traumatic stress disorder. Behav Brain Res. 2014; 268: 72-80.

36. Wilson CB, McLaughlin LD, Nair A, Ebenezer PJ, Dange R, Francis J. Inflammation and oxidative stress are elevated in the brain, blood, and adrenal glands during the progression of post-traumatic stress disorder in a predator exposure animal model. PLoS One. 2013; 8: e76146.

37. Sun XR, Zhang H, Zhao HT, Ji MH, Li HH, Wu J, et al. Amelioration of oxidative stress-induced phenotype loss of parvalbumin interneurons might contribute to the beneficial effects of environmental enrichment in a rat model of post-traumatic stress disorder. Behav Brain Res. 2016; 312: 84-92.

38. Liu FF, Yang LD, Sun XR, Zhang H, Pan W, Wang XM, et al. NOX2 mediated-parvalbumin interneuron loss might contribute to anxiety-like and enhanced fear learning behavior in a rat model of post-traumatic stress disorder. Mol Neurobiol. 2016; 53: 6680-6689.

39. Yehuda R. Biology of posttraumatic stress disorder. J Clin Psychiatry. 2001; 62 Suppl 17: 41-46.

40. Maes M, Lin AH, Delmeire L, Van Gastel A, Kenis G, De Jongh R, et al. Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. Biol Psychiatry. 1999; 45: 833-839.

41. von Kanel R, Hepp U, Kraemer B, Traber R, Keel M, Mica L, et al. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J Psychiatr Res. 2007; 41: 744-752.

42. Miller RJ, Sutherland AG, Hutchison JD, Alexander DA. C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study. Cytokine. 2001; 13: 253-255.

43. Prasad KN, Bondy SC. Common biochemical defects linkage between post-traumatic stress disorders, mild traumatic brain injury (TBI) and penetrating TBI. Brain Res. 2014; .

44. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology. 2017; 42: 254-270.

45. Ke S, Hartmann J, Ressler KJ, Liu YY, Koenen KC. The emerging role of the gut microbiome in posttraumatic stress disorder. Brain Behav Immun. 2023; 114: 360-370.

46. He Q, Wang W, Xu D, Xiong Y, Tao C, You C, et al. Potential causal association between gut microbiome and posttraumatic stress disorder. Transl Psychiatry. 2024; 14: 67.

47. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015; 2: 1002-1012.

48. Koizumi S, Inoue N, Sugihara F, Igase M. Effects of collagen hydrolysates on human brain structure and cognitive function: a pilot clinical study. Nutrients. 2019; 12.

49. Huang KF, Hsu WC, Hsiao JK, Chen GS, Wang JY. Collagen-glycosaminoglycan matrix implantation promotes angiogenesis following surgical brain trauma. Biomed Res Int. 2014; 2014: 672409.

50. Chen JH, Hsu WC, Huang KF, Hung CH. Neuroprotective effects of collagen-glycosaminoglycan matrix implantation following surgical brain injury. Mediators Inflamm. 2019; 2019: 6848943.

51. Osiak-Wicha C, Kras K, Tomaszewska E, Muszynski S, Grochecki P, Kotlinska JH, et al. Evaluation of PTSD-induced alterations in bone biomechanics and the protective potential of CE-123 in a Wistar rat model. J Clin Med. 2025; 14.

52. Alquraan L, Alzoubi KH, Hammad H, Rababa'h SY, Mayyas F. Omega-3 fatty acids prevent post-traumatic stress disorder-induced memory impairment. Biomolecules. 2019; 9.

53. Matsuoka Y. Clearance of fear memory from the hippocampus through neurogenesis by omega-3 fatty acids: a novel preventive strategy for posttraumatic stress disorder? BioPsychoSocial Med. 2011; 5: 3.

54. Beltz BS, Tlusty MF, Benton JL, Sandeman DC. Omega-3 fatty acids upregulate adult neurogenesis. Neurosci Lett. 2007; 415: 154-158.

55. Calderon F, Kim HY. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. J Neurochem. 2004; 90: 979-988.

56. Matsuoka Y, Nishi D, Nakaya N, Sone T, Hamazaki K, Hamazaki T, et al. Attenuating posttraumatic distress with omega-3 polyunsaturated fatty acids among disaster medical assistance team members after the Great East Japan Earthquake: the APOP randomized controlled trial. BMC Psychiatry. 2011; 11: 132.

57. Yamada D, Takeo J, Koppensteiner P, Wada K, Sekiguchi M. Modulation of fear memory by dietary polyunsaturated fatty acids via cannabinoid receptors. Neuropsychopharmacology. 2014; 39: 1852-1860.

58. Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry. 2002; 51: 189-192.

59. Matsumura K, Noguchi H, Nishi D, Hamazaki K, Hamazaki T, Matsuoka YJ. Effects of omega-3 polyunsaturated fatty acids on psychophysiological symptoms of post-traumatic stress disorder in accident survivors: a randomized, double-blind, placebo-controlled trial. J Affect Disord. 2017; 224: 27-31.

60. Ginty AT, Conklin SM. Preliminary evidence that acute long-chain omega-3 supplementation reduces cardiovascular reactivity to mental stress: a randomized and placebo-controlled trial. Biol Psychol. 2012; 89: 269-272.

61. Charney DS, Deutch AY, Krystal JH, Southwick SM, Davis M. Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry. 1993; 50: 295-305.

62. Murrough JW, Huang Y, Hu J, Henry S, Williams W, Gallezot JD, et al. Reduced amygdala serotonin transporter binding in posttraumatic stress disorder. Biol Psychiatry. 2011; 70: 1033-8.

63. Oglodek EA. Changes in the serum concentration levels of serotonin, tryptophan and cortisol among stress-resilient and stress-susceptible individuals after experiencing traumatic stress. Int J Environ Res Public Health. 2022; 19.

64. Lokshina Y, Nickelsen T, Liberzon I. Reward processing and circuit dysregulation in posttraumatic stress disorder. Front Psychiatry. 2021; 12: 559401.

65. Torrisi SA, Leggio GM, Drago F, Salomone S. Therapeutic challenges of post-traumatic stress disorder: Focus on the dopaminergic system. Front Pharmacol. 2019; 10: 404.

66. Nair J, Singh Ajit S. The role of the glutamatergic system in posttraumatic stress disorder. CNS Spectr. 2008; 13: 585-91.

67. Joca SR, Ferreira FR, Guimaraes FS. Modulation of stress consequences by hippocampal monoaminergic, glutamatergic and nitrergic neurotransmitter systems. Stress. 2007; 10: 227-49.

68. Nishi D, Hashimoto K, Noguchi H, Hamazaki K, Hamazaki T, Matsuoka Y. Glutamatergic system abnormalities in posttraumatic stress disorder. Psychopharmacology (Berl). 2015; 232: 4261-8.

69. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG. Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. Neurosci Lett. 2017; 649: 147-55.

70. Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry. 1997; 154: 624-9.

71. Meyerhoff DJ, Mon A, Metzler T, Neylan TC. Cortical gamma-aminobutyric acid and glutamate in posttraumatic stress disorder and their relationships to self-reported sleep quality. Sleep. 2014; 37: 893-900.

72. Gao J, Wang H, Liu Y, Li YY, Chen C, Liu LM, et al. Glutamate and GABA imbalance promotes neuronal apoptosis in hippocampus after stress. Med Sci Monit. 2014; 20: 499-512.

73. Lee B, Lee H. Systemic administration of curcumin affects anxiety-related behaviors in a rat model of posttraumatic stress disorder via activation of serotonergic systems. Evid Based Complement Alternat Med. 2018; 2018: 9041309.

74. Nakahara J, Masubuchi Y, Takashima K, Takahashi Y, Ichikawa R, Nakao T, et al. Continuous exposure to amorphous formula of curcumin from the developmental stage facilitates anti-anxiety-like behavior and fear-extinction learning in rats. Nutr Res. 2021; 85: 99-118.

75. Zhang ZS, Qiu ZK, He JL, Liu X, Chen JS, Wang YL. Resveratrol ameliorated the behavioral deficits in a mouse model of post-traumatic stress disorder. Pharmacol Biochem Behav. 2017; 161: 68-76.

76. Li G, Wang G, Shi J, Xie X, Fei N, Chen L, et al. Trans-resveratrol ameliorates anxiety-like behaviors and fear memory deficits in a rat model of post-traumatic stress disorder. Neuropharmacology. 2018; 133: 181-8.

77. Alzoubi KH, Shatnawi AF, Al-Qudah MA, Alfaqih MA. Vitamin C attenuates memory loss induced by post-traumatic stress-like behavior in a rat model. Behav Brain Res. 2020; 379: 112350.

78. Ahmed M, Alzoubi KH, Khabour OF. Vitamin E prevents the cognitive impairments in post-traumatic stress disorder rat model: Behavioral and molecular study. Psychopharmacology (Berl). 2020; 237: 599-607.

79. Weggen JB, Darling AM, Autler AS, Hogwood AC, Decker KP, Imthurn B, et al. Impact of acute antioxidant supplementation on vascular function and autonomic nervous system modulation in young adults with PTSD. Am J Physiol Regul Integr Comp Physiol. 2021; 321: R49-R61.

80. Prasad KN. Simultaneous activation of Nrf2 and elevation of antioxidant compounds for reducing oxidative stress and chronic inflammation in human Alzheimer's disease. Mech Ageing Dev. 2016; 153: 41-7.

81. Prasad KN. A micronutrient mixture with collagen peptides, probiotics, cannabidiol, and diet may reduce aging, and development and progression of age-related Alzheimer's disease, and improve its treatment. Mech Ageing Dev. 2023; 210: 111757.

82. Jaramillo MC, Zhang DD. The emerging role of the Nrf2-Keap1 signaling pathway in cancer. Genes Dev. 2013; 27: 2179-91.

83. Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, et al. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem Biophys Res Commun. 1997; 236: 313-22.

84. Hayes JD, Chanas SA, Henderson CJ, McMahon M, Sun C, Moffat GJ, et al. The Nrf2 transcription factor contributes both to the basal expression of glutathione S-transferases in mouse liver and to their induction by the chemopreventive synthetic antioxidants, butylated hydroxyanisole and ethoxyquin. Biochem Soc Trans. 2000; 28: 33-41.

85. Ramsey CP, Glass CA, Montgomery MB, Lindl KA, Ritson GP, Chia LA, et al. Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol. 2007; 66: 75-85.

86. Chen PC, Vargas MR, Pani AK, Smeyne RJ, Johnson DA, Kan YW, et al. Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: Critical role for the astrocyte. Proc Natl Acad Sci U S A. 2009; 106: 2933-8.

87. Xi YD, Yu HL, Ma WW, Ding BJ, Ding J, Yuan LH, et al. Genistein inhibits mitochondrial-targeted oxidative damage induced by beta-amyloid peptide 25-35 in PC12 cells. J Bioenerg Biomembr. 2011; 43: 399-407.

88. Suh JH, Shenvi SV, Dixon BM, Liu H, Jaiswal AK, Liu RM, et al. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci U S A. 2004; 101: 3381-6.

89. Trujillo J, Chirino YI, Molina-Jijon E, Anderica-Romero AC, Tapia E, Pedraza-Chaverri J. Renoprotective effect of the antioxidant curcumin: Recent findings. Redox Biol. 2013; 1: 448-56.

90. Kode A, Rajendrasozhan S, Caito S, Yang SR, Megson IL, Rahman I. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2008; 294: L478-88.

91. Gao L, Wang J, Sekhar KR, Yin H, Yared NF, Schneider SN, et al. Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3. J Biol Chem. 2007; 282: 2529-37.

92. Song J, Kang SM, Lee WT, Park KA, Lee KM, Lee JE. Glutathione protects brain endothelial cells from hydrogen peroxide-induced oxidative stress by increasing Nrf2 expression. Exp Neurobiol. 2014; 23: 93-103.

93. Ji L, Liu R, Zhang XD, Chen HL, Bai H, Wang X, et al. N-acetylcysteine attenuates phosgene-induced acute lung injury via up-regulation of Nrf2 expression. Inhal Toxicol. 2010; 22: 535-42.

94. Choi HK, Pokharel YR, Lim SC, Han HK, Ryu CS, Kim SK, et al. Inhibition of liver fibrosis by solubilized coenzyme Q10: Role of Nrf2 activation in inhibiting transforming growth factor-beta1 expression. Toxicol Appl Pharmacol. 2009; 240: 377-84.

95. Schrader C, Ross A. A review of PTSD and current treatment strategies. Mo Med. 2021; 118: 546-51.

96. Linden M, Schermuly-Haupt ML. Definition, assessment and rate of psychotherapy side effects. World Psychiatry. 2014; 13: 306-9.

97. Barlow DH. Negative effects from psychological treatments: A perspective. Am Psychol. 2010; 65: 13-20.

98. Lilienfeld SO. Psychological treatments that cause harm. Perspect Psychol Sci. 2007; 2: 53-70.

99. Sartor Z, Kelley L, Laschober R. Posttraumatic stress disorder: Evaluation and treatment. Am Fam Physician. 2023; 107: 273-81.

100. Watkins LE, Sprang KR, Rothbaum BO. Treating PTSD: A review of evidence-based psychotherapy interventions. Front Behav Neurosci. 2018; 12: 258.

101. Back SE, McCauley JL, Korte KJ, Gros DF, Leavitt V, Gray KM, et al. A double-blind, randomized, controlled pilot trial of N-acetylcysteine in veterans with posttraumatic stress disorder and substance use disorders. J Clin Psychiatry. 2016; 77: e1439-46.

102. Atalay S, Jarocka-Karpowicz I, Skrzydlewska E. Antioxidative and anti-inflammatory properties of cannabidiol. Antioxidants (Basel). 2019; 9.

103. Alway Y, Gould KR, McKay A, Johnston L, Ponsford J. The evolution of post-traumatic stress disorder following moderate-to-severe traumatic brain injury. J Neurotrauma. 2016; 33: 825-31.