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Mini Review

Potential of an antioxidant combination Twendee X® to treat depressive disorders

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Abstract

Depression and other neuropsychiatric disorders have major impacts on the daily life. These disorders are triggered by stress and obstacles stemming from changes in people's environment, relationships, finances, health, or in the case of many women, triggered by childbirth. An increase in the incidence of depression worldwide strongly correlates with modernization, economic downturns and the effects of major global events such as war and the COVID-19 pandemic. Despite the cause of the onset of depressive conditions, there is evidence that implicates Oxidative Stress (OS) as one of the major causes of depressive disorders. This strong association likely stems from the fact that compared to other organs, the brain is more vulnerable OS due to its high oxygen consumption, high lipid content, and weak antioxidant defense. In fact, decreased serum levels of antioxidants and a significant increase in MDA, a marker of lipid peroxidation, have been observed in depressed patients, indicating an elevated OS state. This state leads to not only cellular damage, but also inflammation and mitochondrial dysfunction. Therefore, addressing this lack of antioxidants could potentially alleviate depressive symptoms due to OS. Twendee X® (TwX) is a supplement that combines potent levels of eight active ingredients and has shown preventive effects in Alzheimer's Disease (AD). Studies using diabetes and aged mouse models, known risk factors for dementia, have shown that TwX has antioxidant capacity and mitochondrial protective effects, as well as inhibiting the age-related decline of neurogenesis and autophagy function. We theorized that these actions of TwX have been proposed to benefit depression by controlling OS. This literature review uses publications on PubMed and Google Scholar to explore the role of OS in psychiatric disorders and recent evidence of the therapeutic effects of antioxidants on such disorders. Publications also include those targeting TwX, which we theorize may be effective in neuropsychiatric disorders via its ability to possibly alleviate the effect of OS in the brain.

Introduction

Depression is one of the most common mental disorders affecting cognitive function, quality of life, and overall health, and is characterized by a wide spectrum of symptoms such as insomnia, fatigue, and low self-esteem; persistent emotional symptoms such as guilt and apathy; and physical symptoms such as loss of energy. Depression has been reported to coexist with conditions such as diabetes, anxiety [1,2], Alzheimer's Disease (AD), and schizophrenia [3,4]. Vary antidepressants are used to treat depressive conditions individually, or in combination with one, or several other medications; however, these medications do not always allow patients to achieve complete remission. This can lead to increase in economic burden, addiction to medications, side effects, and the emergence of suicidal thoughts in some cases.

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Oxidative Stress (OS) plays an important role in depressive disorders. Increased Reactive Oxygen Species (ROS) and OS-induced dysfunction are associated with the etiology and progression of these disorders [5-7]. Antioxidant therapy using effective antioxidant combination products that are not defined as pharmaceuticals holds promise in terms of diversifying treatment options for depression.

OS and neuropsychiatric disorders

OS has been associated with a wide range of illnesses, including brain disorders such as neuropsychiatric and neurodegenerative diseases. The influence of OS becomes more pronounced with age. However, in aerobic Organisms OS is elevated regardless of age when stress from environmental, psychological, or socioeconomic factors creates an imbalance in the antioxidant capacity of the organism.

In depressed patients, along with a decrease in total antioxidant capacity, decreased plasma concentrations of antioxidants such as vitamin E, vitamin C, tryptophan, tyrosine, albumin, zinc, glutathione, and CoQ10, as well as decreased antioxidant enzyme activity have been reported [7-9]. Moreover, in patients with Major Depressive Disorder (MDD), increased serum MDA levels [10] and urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels have been confirmed, as well as oxidative damage to DNA by ROS [11]. Additionally, the prevalence of depression is markedly increased in diabetic patients, a disease which is widely acknowledged as being OS driven [12]. All together, these findings strongly support the theory that OS is closely associated with depressive conditions.

ROS is a general term for radical or non-radical oxygen derivatives. Due to their high reactivity, ROS interacts with multiple biomolecules and other substances, causing chain reactions that ultimately damage cellular structures [13,14]. The mitochondria, the main production site of ROS, plays a critical role in energy production, regulation of Ca^{2+} levels, maintenance of ROS levels, and maintenance of cell stability by regulating apoptosis.

Many subunit syntheses of mitochondrial respiratory chain complexes (except complex II) are based on mitochondrial genes (mtDNA), and ROS have a significant effect on the transcription of proteins and RNAs encoded by mtDNA. Therefore, mitochondria with oxidized mtDNA dysfunction and produce large amounts of ROS. This can cause a vicious cycle of ROS and mitochondrial dysfunction, ultimately leading to severe nuclear DNA damage and cell death [15]. Furthermore, increased OS activates inflammatory signaling pathways, resulting in a synergistic effect of OS and inflammation that trigger a vicious cycle.

According to recent studies, depression is associated with changes in brain function, neuronal plasticity, and decreased volume of the frontal cortex and hippocampus [16]. In MDD, OS is one of the main causes of structural and functional changes in the brain and preclinical and clinical studies have reported that increased ROS generation and depletion of antioxidant defenses are responsible for changes in brain structure [17-19]. OS is also associated with increased inflammatory cytokine levels and decreased nerve growth and subsequent neural progression. The production of the inflammatory markers interleukin (IL)-1 and IL-18, the formation of pores in the cell membrane, and the leakage of substances from the cell all contribute to cell death [20,21]. Additionally, to this, cellular senescence and excessive metabolic stress have been reported to cause MDD [22].

Mitochondrial dysfunction not only leads to cellular energy deficiency, but may also contribute to impaired neuronal communication and cellular resilience, which in turn leads to mood and psychotic disorders [23,24]. Various types of stress have also been confirmed to decrease hippocampal neurogenesis in adults, leading to depression. Increased mitochondrial genome and mitochondrial proteins are necessary for neuronal differentiation during neuronal development, and mitochondrial dysfunction plays an important role in impaired adult hippocampal neurogenesis in depression [25,26].

Combined, these findings suggest that, in neuropsychiatric disorders, elevated OS contributes to the onset, progression, and recurrence of depression by causing increased inflammation, mitochondrial dysfunction, and impaired neurogenesis.

Antioxidant combination Twendee X® for oxidative stress control and application in neuropsychiatric disorders.

Twendee X® (TwX) is a dietary supplement containing eight active antioxidants: vitamin C, glutamine, cystine, coenzyme Q10, fumaric acid, succinic acid, niacin, and vitamin B2. Composed mainly of water-soluble vitamins and amino acids, it has passed all safety tests (chromosomal aberration test, toxicity test, and mutation test) equivalent to those conducted for pharmaceutical agents.

Treatment with TwX has resulted in positive effects in various OS-associated conditions in mouse models and in clinical trials. To start, TwX was shown to improve cognitive function in mild cognitive impairment patients in a multicenter randomized, double-blind, placebo-controlled intervention clinical trial [27]. In a mouse model of ischemic stroke, pretreatment with TwX (20 mg/kg/d) for 14 days reduced not only infarct size, but also OS markers, tumor necrosis factor-α (TNF-α), and inflammation markers [28]. In AD model mice with Chronic Cerebral Hypoperfusion (CCH) (CCH + APP23 mice), TwX improved motor coordination and working memory and restored loss of hippocampal neurons. TwX also substantially improved cognitive impairment, reduced Aβ pathology and neuronal loss, and alleviated neuroinflammation and OS [29,30]. In other studies, mice with increased OS due to vitamin E deficiency resulting in compromised cognitive function and coordination, were treated with TwX and showed substantially improved cognitive function and coordination. As well, TwX significantly increased brain-derived neurotrophic factor and nerve growth factor levels in these mice [31]. The effects of TwX on these neurodegenerative diseases have been shown to be protective effects of TwX on mitochondria due to its strong antioxidant capacity, increased ATP production, reduction of OS in blood, maintenance of autophagy function,

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telomere elongation, and maintenance of neurogenesis [32]. In the MCI study mentioned above, TwX did not show any change in affective states as secondary outcomes. As this study solely focused on MCI patients, the results may not necessarily be an accurate reflection of the effects of TwX on depressive symptoms. In fact, Multiple questionnaire results show that taking TwX for 3 - 4 weeks improved in insomnia and fatigue in 80% of participants. Almost 80% of participants also reported a reduction in depressive mood due to improved sleep conditions (https://www.eyez.jp/media/2012_TwendeeX.pdf, https://www.eyez.jp/media/2015_TwendeeX.pdf, Japanese). Thus, the impact of TwX on depression and other neuropsychiatric disorders is worthy of further examination.

Neurodegenerative and neuropsychiatric diseases share a common role for OS, and TwX can reduce OS and inflammatory markers in the brain for neuropsychiatric diseases as well.

There are few therapeutic strategies targeting OS for neuropsychiatric disorders such as depression. There is a growing body of research supporting the therapeutic potential of Ascorbic Acid (AsA), which is one of the antioxidants in TwX. AsA is deficient in stress-related diseases and as a potential neuroprotective agent it offers neuromodulatory and neurotrophic effects. Research exploring this therapeutic option was done with an intraperitoneal administration of high (60 mg/kg) doses of AsA to mice for 3 days. Results showed that this dosage reduced brain acetylcholinesterase activity and improved memory [33,34]. AsA is a water-soluble vitamin and does not accumulate in the body even at high doses. However, there is concern that high doses of AsA produce ascorbyl radical that generate ROS [35,36]. Therefore, using AsA in a way which exploits its therapeutic effects without generating ROS is a challenge, and one that TwX can likely overcome.

TwX contains a well-balanced combination of eight ingredients including AsA. It has significantly higher antioxidant capacity than similar amounts of vitamin C alone and also suppresses ascorbyl radical [37]. Moreover, results have shown that TwX reduced OS and consequent inflammation in the brain as well as increased and maintained neurogenesis at a low dosage of (20 - 40 mg /kg /d) [32] which mitigates concerns of generating ROS.

TwX is likely to support neurogenesis as well as secure cellular energy via protecting mitochondrial function. In addition, as a disease that can trigger and complicate depression, not only in AD but also in diabetes mellitus, TwX effectively reduced the rapid rise in blood glucose levels and suppressed concomitant diabetes.

Conclusion

OS is implicated in not only mild conditions but is also a common causative factor in serious illnesses such as diabetes, neurodegenerative and neuropsychiatric diseases. As such, addressing OS is a logical strategy to treat affected patients. TwX, a dietary supplement that has passed pharmacological safety tests, can assist in this regard. It offers protection via its combination of eight active antioxidants and studies in human and mouse models have demonstrated its efficacy in multiple OS-related diseases.

Since TwX has shown efficacy in neurodegenerative diseases such as AD, it is theorized that TwX may also reduce OS and inflammatory markers associated with neuropsychiatric diseases.

The body has many functions that depend on antioxidants, and oxidative conditions lead to diseases, hence, it is critical for humans to consume a broad spectrum of antioxidants in adequate amounts. OS plays a role in depressive conditions and research has shown it plausible that the effects of oxidative states can be ameliorated with appropriate doses of antioxidants such as those contained in TwX. Hence, neuropsychiatric disorders are suitable targets for TwX and this promising alternative deserves further study and consideration in the treatment of depressive disorders.

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