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Antioxidant supplements as a means to prevent Alzheimer's disease following COVID-19 infection

Suplementy przeciwutleniające jako jedna z metod zapobiegania rozwojowi choroby Alzheimera po przebytym zachorowaniu na COVID-19

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Abstract

Oxidative stress has been proposed as a factor in many conditions, such as Alzheimer's disease. Moreover, there is a link between oxidative stress and a variety of COVID-19 symptoms. The occurrence of multiple diseases can be ascribed to long-term exposure to heightened oxidative stress impeding the body's normal homeostatic function. Complications arising from elevated levels of oxidative stress include lipid peroxidation, mitochondrial dysfunction, protein oxidation, damage to deoxyribonucleic acid (DNA), glycoxidation, weakened antioxidant defence, and impaired amyloid clearance. Moreover, oxidative stress leads to the onset of inflammation through an increase in the levels of active inflammatory factors. It is widely accepted that the prolongation of this detrimental cycle contributes to the development of pathological states. Consequently, interruption of the cycle of oxidative stress is imperative to prevent disease onset. Research has primarily focused on individual antioxidants, with an emphasis on vitamins C and E, owing to their significant properties as antioxidants that help reduce oxidative stress. Compared to individual antioxidants, supplements encompassing a harmonious assortment mixture of multiple antioxidants may be more effective in combating various symptoms associated with pre-existing conditions and current health concerns like COVID-19 and Alzheimer's disease. This review explores the correlation between oxidative stress, COVID-19 infection, and Alzheimer's disease. Additionally, we suggest the use of Twendee X, a remarkably powerful antioxidant compound, to reduce the rate of cognitive decline in individuals with Alzheimer's disease. Moreover, Twendee X can prevent and alleviate COVID-19 and its associated symptoms.

Keywords: Alzheimer's disease (AD), antioxidant, oxidative stress, Twendee X (TwX), COVID-19

Streszczenie

Stres oksydacyjny wymieniany jest jako istotny czynnik w rozwoju wielu schorzeń, m.in. choroby Alzheimera. Istnieje także zależność między stresem oksydacyjnym a objawami COVID-19. Przewlekłe narażenie na wzmożony stres oksydacyjny może mieć związek z występowaniem wielu chorób na skutek zaburzenia prawidłowej homeostazy organizmu. Wśród następstw podwyższonego poziomu stresu oksydacyjnego wymienić należy peroksydację lipidów, zaburzenia czynności mitochondriów, utlenianie białek, uszkodzenia DNA, glikooksydację, osłabienie obronnych mechanizmów przeciwutleniających oraz upośledzenie usuwania amyloidu. Stres oksydacyjny indukuje także stany zapalne na skutek wzrostu poziomu aktywnych czynników zapalnych. Panuje zgodność, że przedłużający się szkodliwy cykl procesów, u podłoża których leży stres oksydacyjny, przyczynia się do rozwoju patologii. Przerwanie tego cyklu jest zatem warunkiem koniecznym, aby zapobiegać wielu chorobom. Dotychczasowe badania skupiały się głównie na poszczególnych antyoksydanatach, a zwłaszcza na witaminie C i witaminie E ze względu na ich znaczące właściwości przeciwutleniające, które pomagają w obniżaniu poziomu stresu oksydacyjnego. W porównaniu z pojedynczymi przeciwutleniaczami suplementy zawierające dobrze zbilansowane połączenie kilku składników o działaniu przeciwutleniającym mogą być bardziej skuteczne w łagodzeniu objawów związanymi z szeregiem schorzeń, m.in. COVID-19 i chorobą Alzheimera. W przedstawionej pracy przeglądowej poddano analizie zależność między stresem oksydacyjnym, zachorowaniem na COVID-19 i chorobą Alzheimera. Wskazano także, że suplement Twendee X, który odznacza się wyjątkowo silnymi właściwościami przeciwutleniającymi, może przyczyniać się

do spowolnienia procesu pogorszenia funkcji poznawczych u osób z chorobą Alzheimera. Istnieją ponadto przesłanki wskazujące, że preparat Twendee X może wpływać na zapobieganie i łagodzenie objawów towarzyszących zachorowaniu na COVID-19.

Słowa kluczowe: choroba Alzheimera (AD), przeciwutleniacze, stres oksydacyjny, Twendee X (TwX), COVID-19

INTRODUCTION

Alzheimer's disease (AD), a debilitating neurodegenerative disorder, stands prominently among these conditions, with oxidative stress implicated in its aetiology and progression (Schneider et al., 2009). Moreover, the global outbreak of COVID-19 has shed new light on the intricate interplay between oxidative stress and viral infections. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for COVID-19, not only affects the respiratory system but also poses potential threats to the central nervous system, with implications for neurodegenerative diseases such as AD (Ciaccio et al., 2021).

This review seeks to unravel the multifaceted connections between oxidative stress, AD, and COVID-19. As we delve into the intricate molecular and cellular mechanisms linking these conditions, we explore potential interventions, with a particular focus on Twendee X (TwX), a robust antioxidant compound (Tadokoro et al., 2020). Our investigation aims to elucidate the promising role of TwX in mitigating cognitive decline in AD and potentially alleviating COVID-19 symptoms.

The following sections will address the neuropathological characteristics of AD (Serrano-Pozo et al., 2011), the impact of oxidative stress on cognitive dysfunction (Padurariu et al., 2010), the link between AD and COVID-19 (Mok et al., 2020), and the role of oxidative stress in the context of the ongoing pandemic (Bakadia et al., 2021). We then introduce TwX, evaluating its therapeutic potential based on clinical evidence and comprehensive antioxidant profile. The conclusion will synthesise these findings, emphasising the significance of antioxidants in combating oxidative stress-related diseases and the potential of TwX as a promising intervention (Kusaki et al., 2017). By dissecting the intricate relationships between oxidative stress, AD, and COVID-19, this review endeavours to contribute to our understanding of potential therapeutic avenues and preventive strategies in the face of complex health challenges.

AD AND OXIDATIVE STRESS

AD is a neurological disease associated with severe cognitive and memory disorders. It is also one of the most prevalent aetiologies of amnesia in the geriatric population (Schneider et al., 2009). The disease has two important neuropathological characteristics: one is the accumulation of plaques in the extracellular part of neurons, with beta-amyloid (Aβ) peptides being the main components of these plaques, while the other is the creation of neurofibrillary tangles inside neurons, which is caused by hyperphosphorylation of tau proteins (Thal et al., 2015). They are observed in the hippocampus and other areas of the cerebral cortex (Nisbet et al., 2015; Thal et al., 2015).

Oxidative stress is a widely recognised contributing factor and a significant component of the process of aging as well as the advancement of various neurodegenerative disorders, such as AD. Thus, oxidative stress has been identified as a promising therapeutic target for the treatment of AD. High oxidative stress arises from an excess of reactive oxygen species (ROS) in the body beyond the available supply of antioxidants to counteract them. This imbalance in ROS production has the potential to compromise biochemical cascades within neurons, ultimately leading to a deterioration of neuronal plasticity and an acceleration of the aging process. Heightened production of ROS that often accompanies age- and disease-related mitochondrial dysfunction, disrupted metal homeostasis, and compromised antioxidant defences has a direct impact on the presence of synaptic activity and the release of neurotransmitters in neurons, leading to cognitive dysfunction. Abnormalities in cellular metabolism can induce the process of generating and gathering amyloid β (Aβ) and hyperphosphorylated tau protein exacerbates mitochondrial dysfunction and promotes the production of ROS, ultimately leading to a detrimental cycle (Tönnies and Trushina, 2017).

ROS is the primary determinant in this context, which results from oxidative stress. The body's immune system is activated by the accumulation of leukocytes and phagocytosis to fight against the invasion of viruses and bacteria. The human body produces ROS naturally in response to exposure to various environmental factors like air pollution, UV radiation, aging, smoking, alcohol consumption, and diet.

Mitochondria and leukocytes serve as the principal locations for the generation of adenosine triphosphate (ATP) and the production of active oxygen. As a result of increased oxidative stress, these immune cells experience a decline in ATP production, leading to a decrease in their ability to function properly. The nervous system is particularly prone to oxidative stress because of its dependence on oxygen and high levels of unsaturated fatty acids and iron. Postmortem examinations of Alzheimer's patients have found considerable oxidative damage to proteins and lipids and in the brain, as well as a noticeable decrease in ATP production and neuronal cell depletion. Moreover, specialists have established a correlation between mild cognitive impairment and elevated oxidative damage occurring in symptoms commonly associated with dementia (Praticò et al., 2002; Tadokoro et al., 2020).

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AD AND COVID-19

COVID-19, which has triggered the global pandemic, is caused by a type of human coronavirus (HCoV) called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The angiotensin-converting enzyme-2 receptors found on both glial cells and neurons provide a pathway for SARS-CoV-2 to enter the central nervous system (Ciaccio et al., 2021; Rai et al., 2022). The cytokine storm syndrome caused by COVID-19 leads to dysregulation of cytokines, resulting in increased production of proinflammatory cytokines. This increase appears to be a factor in the development of chronic neuroinflammation and the onset of neurodegenerative diseases like Parkinson's disease, multiple sclerosis, and AD.

AD patients have suffered considerably due to the direct effects of the virus during the initial phases of the COVID-19 pandemic. Viruses can damage neurons and cause dysfunction, such as the release of neurotransmitters, death by cell lysis or induction of apoptosis, or indirectly activate the immune response against infected cells, thereby initiating the process of neurodegeneration. Chronic inflammation floods the brain with pro-inflammatory elements, damaging neurons and causing associated brain ischemia or other health problems. These symptoms indicate nerve tissue damage that increases the incidence of neurological disorders and contributes to dementia (Abate et al., 2020; Barbieri et al., 2022; Brown et al., 2020).

COVID-19 AND OXIDATIVE STRESS

All members of the family of human coronaviruses (CoVs), including SARS-CoV-2, are opportunistic pathogens of the central nervous system (CNS). Studies have shown that SARS-CoV-2 can infect humans through direct neurotoxicity or indirectly through activation. Damage caused by the host's immune response results in demyelination, neurodegeneration, and cellular senescence in the CNS. Therefore, it can accelerate the aging process of the brain and the development of neurological diseases, including dementia (Lima et al., 2020).

Persistent oxidative stress, as indicated by an elevation in mitochondrial superoxide and lipid peroxidation, has been linked to inflammasome activation, both of which contribute significantly to the severity of the disease (Lage et al., 2022). The concept of oxidative stress refers to an imbalance between the concentration or activity of antioxidants and increased levels of ROS, resulting in cellular harm (Preiser, 2012). ROS play a dual role in the pathophysiology of the infectious process, both as a cause and an effect (Carr and Maggini, 2017). The potent mechanism of ROS production can combat infections effectively, but excessive ROS production may lead to tissue damage, thereby causing harm to organs, endothelial dysfunction, lymphocyte dysfunction, and heightened inflammation (Carr and Maggini, 2017; Jensen et al., 2021). Moreover, the process of inflammation and thrombosis significantly contributes to the restoration of ROS, resulting in a harmful sequence of oxidative stress, inflammation, and aggravation of pathological conditions. The release of pro-inflammatory cytokines such as IL-1β, IL-6, TNF, and IL-8 from immune cells in patients with COVID-19 leads to the development of a cytokine storm and an increase in levels of IL-1 and IL-6 (Petrushevska et al., 2021).

High levels of these cytokines can damage cellular mechanisms by causing widespread inflammation (Lima et al., 2020). Even after the viral load has decreased to undetectable levels, the persistence of elevated oxidative stress levels among recovered patients may result in the manifestation of other conditions, such as COVID-19 sequelae (Cecchini and Cecchini, 2020). Moreover, recent studies suggest that the lipid nanoparticles (LNPs) used in mRNA-based COVID-19 vaccines act as a protective mechanism but also possess strong inflammatory properties that may explain the adverse reactions experienced by some individuals after receiving the vaccine (Hardan et al., 2021; Jackson et al., 2020; Ndeupen et al., 2021). The immune response elicited by COVID-19 and the associated excessive inflammatory processes have the potential to accelerate the progression of inflammation-related neurodegenerative conditions in the brain. This is particularly critical because older patients with dementia have a greater susceptibility to the severe outcomes of SARS-CoV-2 infection, and are thus at an increased risk of developing comorbidities. Neuroinflammation plays a significant role in the pathogenesis of AD (Hardan et al., 2021).

TWENDEE SUPER ANTIOXIDANT COMPLEX

Twendee X® (TwX; TIMA Japan, Osaka, Japan), hereinafter referred to as TwX, is a patented dietary supplement that combines eight types of antioxidants: coenzyme Q10, niacinamide, L-cysteine, ascorbic acid, succinic acid, fumaric acid, L-glutamine, and riboflavin, which provide significant antioxidant and anti-inflammatory benefits (Tadokoro et al., 2020).

Similar to conventional pharmacological medications, TwX has successfully undergone various safety studies, including chromosomal aberration, toxicity, and mutation tests. Due to the abnormal accumulation of Aβ and the deposition of neurofibrillary tangles in the brains of AD patients during oxidative damage, antioxidant drug therapy has been investigated as a potential treatment for AD (Tadokoro et al., 2020).

In an animal study, supplementation with TwX (20 mg/kg/day, from 4.5 to 12 months) was shown to result in reduced ROS levels, improved cognitive abilities, reduced Aβ deposition, tau hyperphosphorylation and tau deposition (Liu et al., 2019a; Rai et al., 2022; Tadokoro et al., 2019). Dietary supplements are anticipated to mitigate the likelihood of developing dementia (Masaki et al., 2000; Morris et al., 2002). However, it has been determined through systematic reviews

that using a single supplement, such as vitamin C (Forbes et al., 2015; Jia et al., 2008), vitamin B (Butler et al., 2018; Forbes et al., 2015; Jia et al., 2008), vitamin D (Butler et al., 2018), vitamin E (Butler et al., 2018; Forbes et al., 2015; Jia et al., 2008), polyunsaturated fatty acid (Butler et al., 2018; Forbes et al., 2015) or their combination (D'Cunha et al., 2018; Forbes et al., 2015; Jia et al., 2008), does not result in a significant reduction in cognitive decline.

However, in 2019, a prospective, randomised, double-blind, placebo-controlled intervention clinical trial found that TwX prevented the progression of mild cognitive impairment (MCI), the pre-dementia stage, cognitive impairment to severe forms of AD (Tadokoro et al., 2019). Other studies have revealed that TwX demonstrates clinical and pathological benefits in animal models of both AD and ischemic stroke, due to its potent antioxidant properties (Brown et al., 2020; Kusaki et al., 2017; Rai et al., 2022). The acute cerebral ischemia model in mice has shown TwX to exert neuroprotective properties by reducing the levels of oxidative stress and inflammatory markers, thereby resulting in the mitigation of ischaemic infarction (Abate et al., 2020).

Further examination has demonstrated that hydrogen peroxide amplified intracellular and mitochondrial ROS by over 60%. Nevertheless, the administration of 60 μg/mL TwX to the cells diminished ROS to 45% and 63% in body cells and mitochondria, respectively. Furthermore, it was observed that the level of superoxide dismutase (SOD), a highly effective antioxidant, rose by 60% in body cells and 147% in mitochondria. These outcomes provide conclusive evidence that TwX shields mitochondria from oxidative stress and suppresses oxidative stress (Rai et al., 2022). TwX significantly increased the levels of brain-derived neurotrophic factor and nerve growth factor in the cerebral cortex of vitamin E-deficient mice. This result indicates that taking a combined antioxidant supplement may be beneficial to human health even after the onset of oxidative stress (Liu et al., 2019b). Two assessment techniques, namely Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Hasegawa's Dementia Scale (Imai and Hasegawa, 1994), have demonstrated that TwX has a noteworthy impact on the significant improvement of MCI (Abate et al., 2020). Based on the most exacting clinical trials, it is reasonable to conclude that these findings suggest that TwX can effectively decrease the likelihood of developing dementia.

While the potential therapeutic benefits of antioxidant supplements have been extensively explored, it is essential to approach the conclusions with caution, especially concerning long-term effects. There are few studies on TwX, including one study on humans and one review; the rest are animal-based studies. TwX's safety and efficacy need to be approached with caution because there is a lack of human-focused research and acknowledged study limitations. The available human randomised study on TwX, as highlighted by Tadokoro et al., comes with notable limitations, including premature trial termination, hindering a comprehensive evaluation of the supplement's extended effects (Tadokoro et al., 2020). Tadokoro et al. acknowledge the necessity for additional studies, particularly to assess the long-term implications of TwX, a point reinforced by the limitations of their own trial. In summary, while preliminary studies hint at the potential benefits of TwX, the current state of evidence warrants careful interpretation and calls for additional well-designed human trials to substantiate its safety, effectiveness, and long-term impacts, especially in the context of neurodegenerative disorders like AD.

CONCLUSION

There are over 120 diseases associated with oxidative stress, among which AD and conditions linked to COVID-19 infection are merely two examples. The hypothesis that antioxidant supplements can restore bodily balance is explored, noting that while many claim to have therapeutic benefits, only a few have proven effective against oxidative stress-linked illnesses. Unlike earlier supplements, TwX contains sufficient quantities of all the major antioxidants that the body requires. Moreover, it is imperative that supplements are not only generally safe but also safe for prolonged use, as is the case with patients diagnosed with AD. TwX satisfies all of these safety requirements, and its high concentrations of multiple antioxidants strongly imply that TwX has a significant therapeutic potential for the prevention and treatment of oxidative stress-related diseases, including AD and COVID-19. Despite its promise, caution is advised in interpreting TwX's potential. Conclusive statements on efficacy and safety require rigorous, well-designed studies addressing the complexities of long-term treatment of neurodegenerative disorders.

Conflict of interest

The authors declared no conflict of interest.

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Author contributions

Original concept of study: MH, MRF. Writing of manuscript: MH, MRF. Critical review of manuscript: MH. Final approval of manuscript: MH, MRF.

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