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Nutritional Management of Mental Disorders: Potential Role of Dietary Flavonoids and Vitamin E

Eddy E. Owaga[1,*], Abdallah Elbakkoush[2], Masuku Sakhile K. S.[3], Rachael A. Nyang'inja[4]

[1]Institute of Food Bioresources Technology, Dedan Kimathi University of Technology, Nyeri, Kenya. P.O. Box 657-10100, Nyeri, Kenya
[2]Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, No.3 Hsin-hai Rd, Taiwan
[3]Department of Community Health Nursing, Faculty of Health Sciences, University of Swaziland. P. O. Box 369, Mbabane, Swaziland
[4]Department of Mathematics and Computer Studies, Kisumu Polytechnic, P.O. Box 143-40100, Kisumu, Kenya

Abstract The increased prevalence of mental disorders is a major public health concern in both the developing and developed world. The pathogenesis of cognitive impairment and mental disorders are largely attributed to the oxidative damage and neuroinflammation in memory-related brain cells and tissues resulting in reduced efficiency in brain functions. Several epidemiological studies show flavonoids and vitamin E may reduce the neuronal damage leading to improved mental health, and the underlying mechanisms for these effect include their antioxidant properties, neuroprotective action in the brain tissues by protecting the neurons against injury, activation of synaptic signalling by enhancing neuronal regeneration and stimulation of the synaptic plasticity; and improvement of the cerebrovascular peripheral blood flow. Thus, this paper emphasizes the potential role of nutritional interventions as a promising strategy towards improving cognitive function and mental health. In particular, we broadly review the evidence for the potential role of flavonoids and vitamin E in modulating cognitive function and psychiatric health. We further examine the potential underlying cellular and molecular mechanisms for their effects in brain function and improved mental health.

Keywords Mental disorders, Flavonoids, Vitamin E, Mild cognitive impairment, Nutrition

1. Introduction

Due to the increased life-time burden of cognitive and mental disorders in both the developing and developed world, there's a growing public health concern on how the mental health complications can be prevented or appropriately managed. For instance in the United States, an estimated 26.2% of those aged above 18 years suffer from a diagnosable cognitive and mental disorder (Lifetime Diagnostic and Statistical Manual (DSM) criteria IV anxiety, mood, impulse-control, and substance use) in as evidenced in data obtained from face-to-face interviews conducted between February, 2001 and April, 2003 [1]. Mental disorders are broadly categorized into cognitive impairment, neurodegenerative or psychiatric disorders and may include: anxiety disorder, cognitive decline, autism, attention deficit/hyperactivity disorder, bipolar disorder and depression; schizophrenia, obsessive compulsive disorder (OCD), attention-deficit/ hyperactivity disorder (ADHD), substance abuse, autism, mild cognitive impairment (MCI) and Alzheimer's disease (AD) [2]. Alzheimer's disease is a neurodegenerative disorder characterized by loss of memory as well as other cognitive abilities due to the presence of neurofibrillary tangles, senile plaques, impaired synaptic function, and cell loss in the brain [3, 4]. On the other hand, MCI is an intermediate state between normal aging and AD, in which there is cognitive impairment not yet severe enough to impair normal daily functioning [5, 6].

The pathogenesis of mental health disorder is associated with multi-dimensional factors that directly or indirectly influence the optimal brain function conditions. The most recognized factors include neuronal inflammation [7, 8] and the generation oxidative damage of memory-related brain cells and tissues [9]. The brain is susceptible to oxidative damage because of the modest antioxidant capacity leading to lipid peroxidation of receptors, enzymes, ion channels and other membrane proteins [2]. Other plausible reasons include reduced endogenous antioxidants levels such as glutathione due to oxidation of neurotransmitters dopamine, serotonin and norepinephrine [10]. Oxidative stress is generated from the reactive oxygen species (ROS) in the cortex and the hippocampus brain regions of humans and results in oxidation of lipid membranes, oxidation of proteins, DNA, RNA and impaired cellular cell functions [11]. Some of the markers of oxidative stress during early stages of progression mental disorders such as AD and MCI include deposition of β-amyloid protein, elevated 2',7'-dichlorofluorescein (DCF) fluorescence and reduced glutathione levels in the brain [4, 12]. As discussed later in

* Corresponding author:
eowaga@yahoo.co.uk (Eddy E. Owaga)
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this review (see section 3.0), targeting oxidative stress through dietary interventions (flavonoids and vitamin E) may be a promising strategy towards prevention of psychiatric disorders.

1.1. Risk Factors for Cognitive Impairment and Mental Disorders

In recent years, there has been continued recognition of the risk association between dietary behaviour, lifestyle factors (exercise, sleep) and mental illness as evident in several correlational and longitudinal epidemiological studies [2, 10, 13-15]. Diet plays an important role in mental health and development of mental disorders [16]. Some of the nutrition-related risk factors for cognitive impairment include subclinical deficiency in essential nutrients (vitamins C, E; β-carotene, B12, B6, folate) as well as caloric-overload related disorders such as hypercholesterolemia, hypertriacylglycerolemia, hypertensi on, and diabetes [5]. Indeed, a meta-analysis on the relationship between depression, overweight and obesity showed obese subjects had a 55% increased risk of being depressed while depressed subjects had a 58% increased risk of being obese, which implied that being overweight increased the risk of depression [17].

Jacka et al. studied the impact of overall diet patterns on mental health in 1,000 women (ages 20-93 years) over a 12-month period and found traditional Mediterranean diet (consumption of vegetables, fruit, legumes, olive oil, fish, cereals, nuts and seeds; moderate consumption of red wine; and low intakes of processed food, red meat, dairy products and vegetable oils) was associated with a lower risk of major depression, dysthymia, and anxiety disorders [18]. In contrast, a Western diet (characterized by consumption of high-energy processed food with little nutritional value and inadequate intake of foods containing essential nutrients) was associated with higher General Health Questionnaire (GHQ-12) scores, reflecting higher levels of psychological morbidity. These findings imply that a diet rich in processed food may lead to increased rates of depressive illness. In a related prospective Kame Project cohort study, Dai et al., assessed whether consumption of fruit and vegetable juices, containing a high concentration of polyphenols, decreases the risk of incident probable Alzheimer's disease in 1836 Japanese Americans [19]. The researchers found a lower hazard ratio for probable Alzheimer's disease in those who drank juices at least 3 times per week (ratio 0.24) compared with the hazard ratio in those who drank less often than once per week (ratio 0.84) and concluded that fruit and vegetable juices may play an important role in delaying the onset of Alzheimer's disease [19].

Park et al., studied associations between dietary behaviors and learning disabilities and attention-deficit/ hyperactivity disorder (ADHD) in Korean children and reported that high intake of sweetened desserts, fried food, and salt was associated with more learning, attention, and behavioural problems, whereas a balanced diet, regular meals, and a high intake of dairy products and vegetables is associated with less learning, attention, and behavioural problems [13]. In population-based study by Jacka et al., dietary intake of magnesium, folate and zinc was associated with depressive illnesses in women [20]. Altogether, these studies provide vital information on the importance of nutritional management on the patients with psychiatry disorders with emphasis on provision of 'whole foods' especially fruits and vegetables to individuals with psychiatric disorders. Thus, nutritional deprivation and nutritional overload may both differentially influence brain function and mental health, and contribute to psychiatric disorders [21].

Aging is also widely recognized as a major risk factor for cognitive impairment and mental disorders [3]. For instance, the rates of dementia and cognitive impairment increase exponentially with advancing age until about 90 years [9]. Varied reasons have been fronted to explain age-dependent deteriorations in memory and cognition, including the overall decline neuronal populations and synaptic connections over time with ageing [3] as well as decline in the antioxidant capacity of brain tissues leading to dysfunction of key organelles such as mitochondria that support the functioning of the brain cells [6]. Consequently, the increased levels of oxidative damage and inflammation result in nerve cell degeneration, cell death, memory loss and cognitive impairment [10].

2. Nutritional Approaches in Prevention and Management of Mental Disorders

The brain requires essential nutrients from the diet for its optimal structure and function, thereby implying the important role of dietary patterns in mental health. Emerging evidence in recent years has indicated some promise in nutritional supplements such as tryptophan, tyrosine, omega-3 fatty acids, folate, magnesium, s-adenosylmethionine, lecithin and glycine in improving cognitive function and mental health , particularly in major depression, bipolar disorder, schizophrenia, and obsessive compulsive disorder (OCD) mental disorders [22]. In this paper, we particularly review the evidence for the potential role of flavonoids and vitamin E in modulating cognitive function and psychiatric health. We further examine the proposed underlying cellular and molecular mechanisms for their effects in brain function.

2.1. Flavonoids

Flavonoids mainly comprising flavonols, flavonones, flavones, chalcones and anthocynanidins, are amongst the most abundant polyphenolic compounds in some of the foods such as fruits, vegetables, tea, red wine, cocoa beans and grape seeds that characterize the healthy Mediterranean-style diet [23-26]. Several studies using animal models have demonstrated flavonoid-rich foods and

pure flavonoids can modulate learning and memory variables [27, 28]. Besides, various human studies on mental disorders have similarly linked dietary flavonoids with better cognitive performance. For instance, Commenges et al. investigated the association between flavonoid intake and incidence of dementia in a cohort of 1367 subjects above 65 years and found that intake of flavonoids was inversely related to the risk of incident dementia [29]. Furthermore, in the Personnes Agées Quid (PAQUID) study, the investigators prospectively examined flavonoid intake in relation to cognitive function in 1,640 subjects aged 65 years or older and found flavonoid intake was associated with better cognitive performance at baseline and with a better evolution of the performance over time [30]. Nevertheless, other human studies have reported contrasting results on the impact of flavonoids. In a Honolulu–Asia Aging Study examining the association of midlife dietary intake of antioxidants to late-life dementia and its subtypes in 2,459 men aged 45-68 years, it was concluded that intake of β-carotene, flavonoids, and vitamins E and C were not associated with the risk of dementia or its subtypes [31]. In sum, flavonoid is a broad group of polyphenols which different chemical structures and properties that may account for the varying data on the beneficial effects on the mental health. However, there is a common understanding that their effects are dose-depend, thus providing a potential area of investigations on the exact mechanism of specific flavonoid subcategory.

2.2. Vitamin E

Vitamin E is an antioxidant fat-soluble vitamin, mainly present in the brain as tocopherols and tocotrienols, hence its importance in the maintenance of membrane and neuronal integrity [32]. Maes et al. investigated serum vitamin E concentrations in 26 healthy volunteers and 42 major depressed patients and found major depression is accompanied by significantly lower serum vitamin E concentrations, suggesting lower antioxidant defences against lipid peroxidation [33]. Vitamin E is abundant in vegetable oils, cereal grains germ oil, butter, and eggs.

Some epidemiological studies and clinical trials suggest a protective role of vitamin E in delaying the onset of mental disorders. Morris et al. examined whether intake of antioxidant nutrients (vitamins E, C, and carotene) were associated with reduced cognitive decline with age in 2, 889 community residents (aged 65 to 102 years), and found a 36% reduction in the rate of cognitive decline among persons in the highest quintile of total vitamin E intake compared with those in the lowest quintile [34]. Moreover, in the Nurses' Health study aimed at investigating the relationship between high dose antioxidant supplements (vitamins E and C) and cognition amongst 14,968 community-dwelling women, users of both vitamin E or C had significantly better mean cognitive performance than did women who had never used vitamin E nor C and there was a trend of increasingly higher mean scores with increasing durations of use [35]. In another study by Masaki et al., the authors determined whether use of vitamins E and C supplements protects against subsequent development of dementia and poor cognitive functioning in 3,385 men, aged 71 to 93 years [36]. A substantial protective effect was found for vascular dementia in men who consumed both vitamin E and C supplements. However, no protective effect was found for Alzheimer's dementia. In addition, use of either vitamin E or C supplements alone was associated with better cognitive test performance and use of both vitamins E and C had borderline significance among those without dementia. In a controlled trial of vitamin E (2000 IU daily) and selegiline (10 mg daily) treatments in 341 patients with Alzheimer's disease of moderate severity for two years, Sano et al. observed that vitamin E treatment slowed the progression of disease in patients with moderately severe impairment from Alzheimer's disease [37].

In contrast, other studies showed vitamin E has no protective effect on mental health, particularly on MCI and AD development. For instance, Luchsinger et al. studied the effect of intake of antioxidant vitamins (carotenes, vitamins C, E) on AD risk in 980 elderly subjects during a 4 years follow-up and found intake of carotenes and vitamins C or E in supplemental or dietary (non-supplemental) form or in both forms were not related to decreased risk of AD [38]. Besides, Zandi et al. examined the relationship between antioxidant supplements (vitamins E, C) and risk of AD in a cross-sectional and prospective study of 4,740 dementia elderly subjects and found that use of both vitamins E and C was associated with reduced AD prevalence and incidence but there was no protective effect with the use of either vitamin E or C supplements alone [39].

In another study, Petersen et al. examined the efficacy of vitamin E (2000 IU daily) and donepezil (10 mg daily) treatment on mild cognitive impairment in 769 subjects and found there were no significant differences in the probability of progression to Alzheimer's disease in the vitamin E group or the donepezil group compared with the placebo group during the three years of treatment [40]. In the animal models, α-tocopherol reduced the degeneration of hippocampal cells after cerebral ischemia and enhanced the recovery of motor function after spinal cord injury while in hypoxic cultured neurons; α-tocopherol inhibited lipid peroxidation and reduced cell death associated with β-amyloid protein [41].

In sum, the available limited published studies suggest that vitamin E may protect against cognitive impairment and mental disorders, however it is noteworthy that substantial beneficial effects are largely realized when vitamin E is administered in combination with vitamin C. nevertheless, due to the inconsistent data on the effect of vitamin E, concerns have been expressed on appropriate dosage, and the timing of the intervention [42]. Moreover, it has been hypothesized that it might be far too late starting a vitamin E therapy in patients with MCI and AD, in which a large proportion of neurons is already destroyed [43]. Thus, we suggest need to focus further randomized

placebo-controlled clinical trials may focus on the mechanism underlying the synergistic effect of these two antioxidants.

3. Mechanistic Underlying Effects of the Flavonoids and Vitamin E

Using cognitive behavioural testing in humans and animals several studies have provided vital information on the potential mechanisms by which the flavonoids and vitamin E may modulate brain functions and consequently influence mental health. Firstly, due to the distinct role of oxidative damage in the pathogenesis of cognitive impairment and mental disorders, the protective effects have been mainly attributed to the antioxidant properties of flavonoids and vitamin E, which can be achieved via suppressing of the formation of free radical from lipid peroxidation and scavenging of the reactive oxygen species (ROS) [4], and chelation of the metal ions [44]. Recent studies have shown flavonoids can signal gene expression of antioxidant factors such as glutathione and superoxide dismutase through the modulation of Nrf2 (nuclear factor erythroid 2 p45-related factor 2) transcription factor [10]. Vitamin E (α-tocopherol) interacts with cell membranes due to its lipid-solubility and interrupts free radicals chain reaction that cellular membranes [32]. Secondly, flavonoids may confer neuroprotective action in the brain tissues by protecting the neurons against injury induced from neuroinflammation and neurotoxins. Consequently, they promote neuronal survival and function in the brain [3, 12, 24, 25]. Thirdly, flavonoids may activate synaptic signalling by enhancing neuronal regeneration and stimulation of the synaptic plasticity, which is an important mechanism for brain memory functions [44-46]. Lastly, flavonoids can traverse the blood-brain barrier and improve the cerebrovascular peripheral blood flow [45]. This enhanced flow contributes to improved cognitive performance due to the newly induced neuronal growth resulting from the vascular growth factors. Besides, enhanced vascular flow promotes oxygen delivery to the brain regions and hippocampal neurons [10].

4. Conclusions and Future Prospective

Oxidative damage and neuroinflammation in the brain tissues are established pathophysiological factors in mental disorders. Increasing evidence from cognitive behaviour animal and human studies show dietary flavonoids and vitamins E may reduce the neuronal damage leading to improved cognitive performance and mental health. The underlying mechanisms for the improved cognitive performance upon flavonoid and vitamin E consumption are attributed to antioxidant properties, neuroprotective action in the brain tissues by protecting the neurons against injury, activation of synaptic signalling by enhancing neuronal regeneration and stimulation of the synaptic plasticity; and improvement of the cerebrovascular peripheral blood flow. Nevertheless, due to the very limited number of studies linking the effects of flavonoids and vitamin E on the behavioural, physiological, biochemical and molecular aspects of cognitive impairment and mental disorders, we suggest further rigorous study designs on flavonoids and vitamin E alone or in combination with other supplements. Moreover, with the advent of nutrigenomics in management of health and diseases, brain-nutrition-gene interactions is a potential area of further research towards understanding the precise effects of flavonoids and vitamin E.

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