Review article

Diet and depressive disorders

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ABSTRACT

Background: The importance of foods or food constituents in mental health is increasingly recognized, and "nutritional psychiatry" is a growing discipline. **Objective**: This narrative review aims to present work supporting associations between food or food constituents and mental health, specifically depressive disorders. **Methods**: The data presented is derived from preclinical and clinical work, including *in vitro* and *in vivo* assays, as well as observational studies and randomized clinical trials of dietary interventions. The focus of the review is the mediation of inflammatory processes and oxidative stress by dietary constituents that are an integral part of a healthy diet, such as the Mediterranean diet and similar. **Results and Discussion**: We present evidence for the role of the diet in prevention and management of depressive disorders, beyond the effect of individual nutrients. The findings indicate that among the dietary components with higher degree of evidence to influence depressive disorders are long chain n-3 polyunsaturated fatty acids (EPA and DHA), and various dietary bioactive compounds, especially plant-derived secondary metabolites represented by polyphenols such as flavonoids and resveratrol. **Conclusion**: Diet exerts an important role on mental health, and evidence indicates that some dietary constituents contribute to the prevention of depressive disorders.

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Keywords: Diet; Mental health; Depressive disorders; Phenolic compounds; Polyunsaturated fatty acids

Introduction

In ancient Greece, medical treatises already pointed to the dietary intake of fruits, vegetables, nuts, herbs and spices as prescriptions to relieve various ailments at a time when boundaries between the categories 'drugs' and 'foods' were diffuse [1]. Based on this knowledge, Islamic medicine emphasized the influence of mind states and emotions on the genesis of numerous illnesses, proposing diet as the primary means for healing and recuperating the body's equilibrium [2]. The study of the potential impact of an adequate diet on the brain has advanced to the degree that "nutritional psychiatry" has emerged as a research field in its own right [3]. It focuses on the intake of dietary constituents and their effect on mood alterations, mainly depressive disorders (DD) and anxiety disorders [4-6]. Numerous antidepressants are widely available [7] and have an important therapeutic role. However, they cannot ameliorate the spectrum of alterations that occur in DD and are unlikely to be a long-term solution over a lifetime. Further, there are individuals for whom antidepressants are not an option due to troubling side-effects, or therapeutic failure.

DD are common, recurrent disorders, affecting over 300 million people worldwide [8]. Lifestyle choices may constitute an alternative to manage DD, offering an option for individuals that are unable to access to pharmacological therapy or psychotherapy, as well as for those exhibiting mild disorders [9]. Indeed, healthy lifestyle habits should be considered in any medical prescription. Diet is a major environmental health determinant that is susceptible to being modified. Adequate nutrition in all age stages exerts fundamental roles in mental health, since the brain requires macro- and micronutrients to function optimally [10-13]. Inadequate nutrition may augment the risk of developing mood and cognitive alterations by affecting physiological processes including levels of neurotransmitters, function of cell membranes and function of vascular tissue, among others [14]. Although relationships between diet and the development of mood impairment may occur in different scenarios, in the present review we will focus on those affecting inflammatory processes and oxidative stress, as well as the effect of gut microbiota.

Diet and the Central Nervous System

Among the most studied dietary components associated with neurodevelopment, brain function and its impact on DD and anxiety are classical nutrients (tryptophan [15]), certain vitamins (B12 and folic acid [16-18], D [19]), minerals (magnesium [20], zinc [21,22]), taurine [23], and fatty acids [24-26]). More recently, the list has included bioactive compounds that are not necessarily categorized as nutrients, such as phenolic compounds.

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Healthy Diet

A major behavioral factor for men and women that exerts a protective effect on mental health is intake of fruits and vegetables [27]. The Mediterranean Diet (MedD) is recognized to have numerous health properties, and is characterized by abundant plant-derived foods (e.g. fruits, vegetables, pulses, whole grains, nuts, extra virgin olive oil), moderate intake of fish, poultry, dairy, and a low intake of red meats, refined grains, sugar and processed products. This diet supplies a variety of bioactive compounds, such as polyphenols, carotenoids, sulfur compounds, phytosterols, terpenes, among others, many of which exhibit antioxidant activity. Intake of these food constituents has been associated, among various physiological effects, with optimism in adults [28-30]. With regard to mental health, the MedD is a dietary pattern that has been associated with reduced incidence of Alzheimer disease, cognitive impairment and depression compared to a Western diet [31-41]. The latter is characterized by a high content of saturated fats and n-6 polyunsaturated fatty acids (PUFA), meats and processed foods. Indeed, the intake of processed foods has been associated with DD in observational studies [42]. Opie et al. [43] recommend following a "traditional" dietary pattern (e.g. MedD, Norwegian or Japanese) that favors natural and local produce, and limits intake of processed, convenience and ready-to-eat products, among others, considered non-healthy. The MedD contains a variety of tree nuts (walnuts, almonds, pistachios, pine nuts, Brazil nuts, among others), characterized as healthy due to their macronutrient (fats, proteins with a high proportion of arginine) and micronutrient (minerals, vitamins) content, while also supplying various bioactive phytochemicals with a potential beneficial effect on brain function (phenolic acids, flavonoids, stilbenes, isoflavones, lignans, tannins, proanthocyanidines, carotenoids, alkaloids, cumestans, phytates, among others [10,44,45]).

Phenolic Compounds

A healthy diet supplies a myriad of phenolic compounds (PC) that may affect neural function in multiple ways [46]. PC are capable of interacting with intracellular and glial signaling pathways; they modulate brain flux, protect against neurotoxins and neuroinflammation [47,48]. Some neural cells possess PC, GABA [49,50] and opioid receptors [51,52], which may activate pathways related to plasticity and the synthesis of new synaptic routes. Numerous PC have been assayed in preclinical studies for their potential roles as antidepressants [53-55].

Resveratrol (3,4,5-trihydroxy-trans-stilbene) is a widely studied PC found in red/black grapes, peanuts, and derivatives that exhibits pleiotropic actions [56,57]. In preclinical models, resveratrol exerts anti-inflammatory, antioxidant, anti-polimerizing action on amyloid beta, and modulates the action of various molecular effectors that participate in neuronal survival and death, among others [50,58,60,61]. As an anti-inflammatory agent, resveratrol dampens the expression of inflammatory mediators (e.g. receptors RTL4 [62], ATP/P2X7 [63]; cyclooxygenases COX-1, COX-2; and cytokines including TNFα). It is able to influence expression of intracellular mediators such as SIRT-1 [64,65], AMPK [66], and eNOS [67,68], ultimately impacting transcription factors, including NF-κB. Other effects related to the inflammatory response include reduced synthesis of endothelin-1, a potent vasoconstrictor [69].

PC are generally recognized as antioxidants that primarily act by augmenting the activity of antioxidant enzymes including catalase, glutathione peroxidase, and superoxide dismutase [70-72]. In a chronic stress model primarily designed to investigate antioxidant effects of trans-resveratrol, Yu et al. [73] observed an increment of monoamine neurotransmitters (serotonin, noradrenaline and dopamine) that the authors attribute to inhibition of oxidation induced by monoamine-oxidases. Further, Fahim et al. [74] demonstrated that resveratrol reverted depression associated with testicular dysfunction in rats, likewise related to diminished oxidative stress, inflammation and apoptosis, but also, ultimately, restitution of testicular function and increase of testosterone levels. There are many examples of PC with potential to exert beneficial effects on mental health. An outstanding example is quercetin, a flavonoid abundant in a variety of fruits and vegetables (e.g. apples and onions). In addition to exerting classical antioxidant effects generally attributed to PC, quercetin can activate the transcription factor Nrf2, which regulates the expression of endogenous antioxidant proteins [75], and can augment the production of heme oxygenase-1, which is also an antioxidant [76]. Another example, frequently promoted in health claims, is that of flavonoid polyphenols derived from cocoa that are present in high amounts in dark chocolate. These PC exhibit high antioxidant and anti-inflammatory properties [77], and have been shown to exert beneficial effects by preventing neurodegeneration and mood impairment [78]. Jackson et al. [79] analyzed the US National Health and Nutrition Examination Survey (NHANES) data of dietary intake during 2007-2008 and 2013-2014, observing that dark chocolate intake associated with reduced depressive symptoms.
Despite the growing body of evidence supporting the potential effects of PC on neuroprotection, there remains a lack of randomized clinical trials to substantiate these primarily preclinical findings.

Polyunsaturated Fatty Acids

The availability of dietary fatty acids is fundamental for growth, development, and maintenance of the nervous system, particularly long chain polyunsaturated fatty acids (LCPUFA) belonging to both n-3 family (derived from α–linolenic acid [ALA, 18:3n-3]) and n-6 family (derived from linoleic acid [AL, 18:2n-6]). Of particular relevance for neuroprotection are n-3 eicosapentaenoic acid [EPA, 20:5n-3] and docosahexaenoic acid [DHA, 22:6n-3], primarily found in fatty fish and seafood [80,81]. The MedD supplies ALA through seeds and nuts, and encourages consumption of seafood [82]. Indeed, low dietary intake of foods supplying LCPUFA has been associated with DD [83,84].

EPA and DHA incorporate in phospholipids and cholesterol esters embedded in neuronal membranes [85], including myelin and synaptosomes [86], with high amounts of DHA, in particular, in the synaptic, mitochondrial and endoplasmic membranes. Both participate directly in synaptogenesis and synaptic functions, activation of ion channels, modulation of cell signaling mechanisms, including dopaminergic and serotoninergic pathways, neural cell development and remodeling [87-90]. Non-esterified DHA participates in cognition and visual processes [91], through the regulation of gene expression [92].

In their systematic review and meta-analysis, Goldsmith et al. [93] confirm that severe mental illnesses, including major DD and schizophrenia, are associated with higher levels of inflammatory peripheral and systemic biomarkers. DHA modulates inflammation by acting on a variety of transcription factors involved in metabolic pathways [94-96]. Further, EPA and DHA are precursors for a variety of molecules with potent anti-inflammatory effect, including resolvins and neuroprotectins [97-99]. The multiplicity of roles on brain function has led to work evaluating DHA supplementation on neuropsychiatric disorders, including DD, as well as age-related diseases such as Alzheimer's [100-103]. Numerous studies of diverse epidemiological designs, including randomized controlled trials, support the intake of EPA and DHA to improve mood disorders, among which DD predominates [104-107]. There is currently

clinical evidence that n-3 LCPUFA may reduce symptoms of DD [108-113]. Interest on the subject is rapidly rising, as evidenced by a recent increment in research on the topic. Initial clinical trials have evaluated dietary LCPUFA intake with severe DD [114-116] and systematic reviews of observational studies, some with controversial results [117-121], indicate that LCPUFA may exert at least a preventive effect, and might even have a therapeutic role in severe DD [122]. Whether this is definitively attributable to reduction of inflammation is not established [123].

Gut Microbiota

Obesity is highly prevalent in the population globally, and is bidirectionally associated with DD [124,125], with an inflammatory component underlying both pathologies [126], and obesity-associated neuroinflammatory processes have been described [127]. The gut microbiota–brain axis has emerged as a major determinant for the modulation of obesity [128] as well as cognition and behavior [129], including social behaviors and managing stress [130]. Depletion of the microbiota profoundly alters the underlying [130]. Among recent evidence, Huang et al. [131] describe a significant shift of microbial diversity in patients with DD compared to healthy individuals, exhibiting a higher content of pro-inflammatory bacterial genera. In DD, as in all stress-related disorders, hypothalamic-pituitary-adrenal alterations are common, including elevated plasma cortisol, elevated corticotropin releasing factor levels in cerebrospinal fluid and high concentrations of pro-inflammatory cytokines [132]. The persistence of low-grade immune-inflammatory processes are an integral part of the pathophysiology of DD [133], and the role of the gut microbiota-brain axis in these pathophysiological mechanisms is increasingly recognized [134]. Studies involving the manipulation of gut microbiota with probiotics for the prevention and treatment of DD and associated comorbidities are being profusely published [135]; however, the topic is beyond the scope of the present review.

Conclusion

This review addresses the increasing recognition of the relationship between diet and mood disorders, mainly depression. DD affect individuals of all age groups worldwide, and the medical community is increasingly recognizing that the approach to this illness should be more holistic, in contrast to current strategies based primarily on pharmacotherapy. We present evidence for the role of the diet in prevention and management, beyond the effect of individual nutrients. Increasing evidence indicates that dietary constituents exerting beneficial effects on DD include various bioactive compounds with antioxidant and anti-inflammatory effects, including phenolic compounds, and n-3 fatty acids, namely EPA and DHA. These are an integral part of a healthy diet, exemplified by the MedD and similar. The role of the gut-brain axis is briefly covered, though it is noteworthy that healthy diets include constituents that positively affect the amount and diversity of intestinal microbiota; this is an additional argument to emphasize the importance of adequately choosing the foods we eat.

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