

Non-pharmacological approaches for stress-related neuropsychiatric disorders: Focus on physical activity and natural compounds

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Abstract

This editorial emphasizes on non-pharmacological approaches for stress-related neuropsychiatric disorders due to side effects of pharmacological approaches. It highlights various exercises, specific natural compounds and their mechanisms for stress reduction. A combination of both can be a good strategy for the stress management. There are some challenges for these approaches. One major limitation is the standardization of these interventions. Natural compounds often have different quality and potency depending on their source and preparation, which can impact their efficiency. Additionally, determining the optimal dosage for different compounds remains a significant challenge, as individual responses can vary considerably. Interdisciplinary collaboration between researchers, clinicians and policymakers must be established to address the challenges. By conducting large-scale, well-designed clinical trials researchers gain a deeper understanding of the mechanisms underlying these approaches and can prepare clear guidelines for their integration into mainstream healthcare, ultimately improving patient outcomes and reducing dependence on pharmacological treatments.

Key words: inflammation, physical activity, antioxidants, natural compounds, stress-related disorders

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Introduction

Stress is one of the primary risk factors for a range of neuropsychiatric conditions. It is typically defined as an organism's response to environmental challenges aimed at maintaining bodily equilibrium. Prolonged stress activates the hypothalamic–pituitary–adrenal (HPA) axis, triggering significant inflammatory responses.¹ Stress not only affects HPA, but it also impacts neuronal structure, such as hippocampus, amygdala and prefrontal cortex.² The brain is profoundly affected by adverse environmental conditions, as seen in numerous structural and functional maladaptive changes observed in both preclinical models and clinical studies of depression.³ Oxidative stress contributes to neuronal damage, including lipid peroxidation and protein oxidation.⁴ Prolonged exposure to stress can negatively impact cognitive abilities and alter the dendritic architecture of pyramidal neurons in the CA3 region of the rat hippocampus. Furthermore, stress can impair brain development, leading to deficits in adult learning and memory.⁵ Oxidative stress has been implicated in a variety of neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, and neuropsychiatric conditions like schizophrenia, bipolar disorder, anxiety, and depression.⁶ While antidepressants and antipsychotics are widely used to treat neuropsychiatric disorders, they come with significant limitations. Many medications cause side effects, including weight gain, sedation, gastrointestinal issues, and metabolic disturbances, which can reduce patient compliance.⁷ As a result, non-pharmacological approaches offer a promising alternative for treating stress-related disorders. These approaches are gaining attention as effective options for managing and treating stress-related neuropsychiatric conditions.^{4,8} This editorial examines physical activity and natural compounds as potential non-pharmacological treatments for stress-related neuropsychiatric disorders, drawing on the authors' expertise and experience.

Physical activity as a non-pharmacological approach for stress-related neuropsychiatric disorders

A key strategy for reducing the adverse effects of stress is physical activity. Studies have demonstrated that exercise mitigates cognitive impairments and increases brain-derived neurotrophic factor (BDNF) levels, ultimately lowering the risk of neuropsychiatric disorders. The beneficial effects of exercise on brain function are, at least in part, mediated by BDNF.^{9,10} Moradikor et al. investigated the effects of wheel running exercise on adolescent stress-induced anxiety and depressive-like symptoms. Their study demonstrated positive effects in reducing stress and enhancing behavioral responses, primarily by increasing antioxidant capacity and upregulating BDNF expression.¹¹ In another study, the effects of voluntary exercise on stress in female rats were investigated, revealing that exercise reduced

corticosterone levels and increased BDNF expression.⁵ There is also evidence supporting the effects of treadmill exercise in reducing inflammation and enhancing antioxidant status in stressed rats.⁴ A human study examining the effects of various types of physical exercise on stress coping in 9 university students reported that physical exercise alleviates stress by eliciting positive emotions, which, in turn, regulate health behaviors and enhance overall wellbeing.¹² Another study on women reported that physical exercise can decrease psychosocial stress.¹³ This paper mentioned some cases of the positive effects of exercise in decreasing stress. Exercise is not limited only to treadmills; other exercises, such as yoga and walking, can decrease the negative effects of stress. Exercise not only mitigates the negative effects of stress by enhancing antioxidant capacity and reducing inflammation, but it also regulates the HPA axis, lowers cortisol levels and strengthens stress resilience. Additionally, it boosts BDNF levels, promotes neuroplasticity and improves cognitive function. Exercise strengthened the mitochondria in the hippocampus by boosting brain plasticity, lowering cell death and improving stress symptoms.¹⁴ An increase in BDNF levels due to exercise can enhance mitochondrial function, promote neuroplasticity and regulate apoptosis signaling in the hippocampus, contributing to stress reduction. Physical activity, when combined with medication, can improve outcomes in key brain regions such as the amygdala and hippocampus, contributing to better stress management and overall mental health.¹⁴ Exercise may enhance antioxidant levels by activating cellular pathways such as Nrf2, which regulates antioxidant responses. Additionally, physical activity modulates inflammatory factors by decreasing pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) while increasing anti-inflammatory cytokines like interleukin 10 (IL-10). In human models, these mechanisms primarily contribute to improved emotional regulation and stress resilience.

Natural compounds as a non-pharmacological approach for stress-related neuropsychiatric disorders

Natural compounds and their derivatives have been utilized for stress management due to their strong antioxidant properties.¹⁵ These compounds, including medicinal plants, their derivatives and active compounds, help alleviate stress by reducing inflammation, regulating cortisol levels and promoting neuroprotection. Additionally, L-theanine, magnesium and probiotics support mood regulation and improve brain function, offering potential benefits for stress-related neuropsychiatric disorders.^{16,17} Moradikor et al. investigated the effects of *Spirulina platensis* in the treatment of stress and reported its beneficial effects through the upregulation of BDNF and tropomyosin receptor kinase B (TrkB) expression.⁸ In another study, *Spirulina platensis* was shown to improve scopolamine-induced memory deficits by reducing malondialdehyde (MDA) levels

in stressed rats.¹⁸ Coating antioxidants is an effective strategy to enhance their efficiency and bioavailability. Curcumin nano-phytosomes decreased stress by increasing the BDNF and improving antioxidant status.¹⁹ Natural compounds can increase neuroplasticity in the hippocampus, decrease hyperactivity in the amygdala and support emotional regulation in the prefrontal cortex.²⁰ As mentioned, natural antioxidants can have abilities for the management of stress. However, a combination of exercise and natural compounds shows greater efficiency than single approach.^{5,8}

It has been reported that physical exercise increases the release of BDNF and TrkB, which are ultimately delivered to the brain.²¹ There is also evidence showing that physical activity increases hippocampal BDNF expression to a desired level.²² Additionally, BDNF-induced TrkB activation promotes the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathways, which play essential roles in encouraging neuronal survival and synaptic plasticity.²³ Studies have reported the stimulatory effects of exercise on BDNF-induced TrkB activation.²⁴ It has been reported that low-intensity physical exercise increases the mRNA expression of BDNF and neuronal activation in stressed rats.²⁵ The exercise-induced increase in BDNF may result from an increased release of serotonin and/or norepinephrine.²⁶ The effects of exercise might be mediated by an increase in 5-HT/NE neurotransmission, which promotes cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling and the transcription factor cAMP response element-binding protein (CREB). The protein activation enhances the expression and secretion of BDNF, which acts via TrkB receptors. Similarly, *Spirulina platensis* extract, as a natural compound, boosted the activation of both p-ERK (extracellular signal-related protein kinase) and p-CREB proteins, which in turn increased BDNF levels in the hippocampus and improved memory in mice.²⁷ Additionally, non-protein parts of *Spirulina platensis* have been shown to promote BDNF gene activity by activating heme oxygenase-1 in glial cells.²⁸ These results emphasize the importance of BDNF in the positive effects of *Spirulina platensis* on brain function. There are evidences for the effects of other natural compounds on BDNF/TrkB, such as phenols.²⁹ Thus, exercises and natural compounds can work in similar pathways for affecting BDNF/TrkB. On the other hand, acute exercise boosts Nrf2 signaling by reactive oxygen species (ROS) production. Nrf2 is a regulator of antioxidant defenses and regulates expression of more than 200 cytoprotective genes.³⁰ Different compounds can activate the Nrf2-antioxidant responsive element (ARE) pathway, which is responsible for triggering antioxidant responses in cells.^{31,32} This pathway helps decrease the damage caused by free radicals and inflammation, which are key contributors to neurodegenerative diseases and aging. The increase of expression of these molecular pathways, both physical activity and certain compounds can work together to improve brain health and mitigate the negative effects of oxidative stress.

In summary, physical exercise and natural compounds exert anti-stress effects through similar mechanisms, and their combination may serve as an effective strategy for stress management. The synergistic effect of exercise and compounds targeting BDNF-TrkB and Nrf2-ARE pathways can protect against stressful factors and decrease the risk of age-related cognitive decline or neurological disorders. The ability of exercise to enhance BDNF levels can complement the antioxidant effects mediated by Nrf2 activation. However, the effectiveness of these natural compounds may be constrained by challenges such as limited bioavailability, variability in potency and potential adverse effects. These factors can influence their clinical applicability and should be carefully considered when assessing their potential for stress alleviation.

Challenges and future directions

Although studies have highlighted the promising potential of non-pharmacological approaches, such as physical activity and natural compounds, in the treatment of stress-related neuropsychiatric disorders, several challenges remain. One major limitation is the standardization of these interventions. Natural compounds often exhibit variations in quality and potency depending on their source and preparation, which can impact their efficacy. Additionally, determining the optimal dosage for different compounds remains a significant challenge, as individual responses can vary considerably. The long-term effects of these approaches are also not fully elucidated, and further research is essential to investigate their safety and effectiveness over extended periods of use. It is essential to note that most studies have been conducted on rodents, and their results cannot be directly generalized to humans. To address these challenges, further research and clinical validation are essential to ensure the efficacy, safety and standardization of these non-pharmacological approaches. Controlled clinical trials and systematic studies can significantly elucidate the mechanisms by which these interventions exert their effects and provide evidence for their use in clinical practice. The need for large-scale, well-designed studies is essential to ensure that these approaches can be safely integrated into mainstream healthcare. Additionally, further studies must identify and elucidate the possible mechanisms underlying the effects of physical activity and natural compounds on stress-related neuropsychiatric disorders. By building an extensive body of literature, these approaches can be effectively integrated into existing treatment frameworks, with the goal of improving patient outcomes and reducing reliance on pharmacological treatments. Finally, while rodent studies provide valuable insights, their direct applicability to humans is limited. Additionally, challenges remain in designing large-scale clinical trials and addressing regulatory concerns to facilitate the integration of these approaches into mainstream healthcare.

Conclusion

In summary, both physical activity and natural compounds offer promising non-pharmacological strategies for managing stress-related neuropsychiatric disorders. Physical activity, through various forms such as treadmill exercise, yoga and walking, can reduce stress by regulating the HPA axis, decreasing inflammation, improving antioxidant status, and boosting BDNF. These effects enhance stress resilience, cognitive function and overall brain health. Similarly, natural compounds like *Spirulina platensis* and curcumin play significant roles in reducing inflammation, regulating cortisol levels and promoting neuroprotection, further supporting stress management. When combined, physical exercise and natural compounds appear to be more effective than either approach alone, suggesting a synergistic potential for stress management. However, despite their promising effects, several challenges remain unresolved. The standardization of these approaches, including the quality and potency of natural compounds, is a major obstacle. Additionally, determining optimal dosages for individual responses and understanding the long-term effects of these strategies require further research. While most studies have been conducted in animal models, more human-based clinical trials are essential to validate these findings and better understand their clinical relevance. Animal studies provide base information and open a way for future studies on humans. Future research should focus on overcoming these challenges, with interdisciplinary collaboration between researchers, clinicians and policymakers being crucial for advancing these approaches. Large-scale, well-designed clinical trials will be key to providing deeper insights into the underlying mechanisms and establishing clear guidelines for integrating these strategies into mainstream healthcare, ultimately improving patient outcomes and reducing reliance on pharmacological treatments.

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