



REVIEW PAPER

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Nootropics: Phytochemicals with Neuroprotective and Neurocognitive Enhancing Properties

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ABSTRACT

Introduction. Neurological chronic conditions represent a healthcare concern worldwide. They hinder a person's functionality affecting family, social interactions, as well as academic and work performance. In addition, the complexity of these illnesses and the variable response to treatments, as well as the side-effects, call for the research and implementation of phytochemicals known as Nootropics to form part of an integrative treatment.

Aim. To present the influence of nootropics on neuroprotection and neurocognition.

Material and methods. Analysis of literature data found in the PubMed database.

Results. Nootropics, which can be synthetic or natural, possess properties that translate in enhancement of mental or neurocognitive functions. Within the natural options, vitamins, plants and even fungi have been found to produce cognitive enhancement with less side-effects. Continuing research has shown promising therapeutic uses for B vitamins, *Hericium herinaceus* and *Ginkgo biloba* as coadjuvants in the treatment of neurologic chronic conditions to improve an individual's neurocognitive functions and quality of life.

Conclusion. Nootropics open the door for new research, clinical implementation and promotion of integrative health especially in cognitive neuroscience by implementing products of natural sources. This is particularly important in order to identify side-effects, drug-herb interactions, proper posology and synergic actions that may prove to improve neurocognitive functioning and health improvement.

Keywords. cognitive enhancers, phytochemicals, neurologic conditions, B vitamins, *Hericium erinaceus*, *Ginkgo biloba*

Introduction

Attempts to enhance human potential and performance through "potions" dates back from the ancient Greeks and is still present today, especially in light of the high incidence and prevalence of neurological disorders.¹ Cognitive disorders are majorly characterized

by significant memory loss and inability to perform day to day normal activities which affect the life of individuals as well as their caregivers.² These conditions have become an emerging challenge to healthcare systems globally owing to the high burden of disease and lack of health-care infrastructure and resources, particularly in

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low- and middle-income countries.³ The treatment and management of memory loss is highly challenging as no potential remedy is available at present for the complete cure.² At present, there is no potential therapy to cure dementia and although the approved therapies improve the symptoms they cannot modify the course of disease.⁴ In the absence of effective pharmaceutical options for dementia, complementary medicines have been exhaustively explored.⁵

Neurocognitive Disorders

A wide array of acquired neurologic conditions exist that can produce both temporary and chronic cognitive impairment.⁶ In this matter some recovery is expected in conditions like anoxia, stroke or head trauma, whereas Dementia and Multiple Sclerosis are progressive conditions in which a continuous deterioration is expected.⁶

Dementia and Alzheimer's Disease

Dementia is a syndrome comprising over 100 diseases characterized by a decline in cognition that interferes with the various types.⁵ Among these types Alzheimer's disease (AD) has been given great attention due to the level of disability it produces. AD is one of the major causes of dementia in an estimated 60–80% of cases.⁷ According to the Alzheimer's Association 2017 report, about 5.5 million individuals have AD.⁸

Alzheimer's disease is a heterogeneous disorder of multifactorial etiopathogenic factors with divergent clinical symptomatology, various ages of onset, presence or absence of germline mutations, degree and spread of pathological changes, existence or non-existence of risk factors and manifestation or non-appearance of polymorphic susceptibility alleles.⁹ It is characterized by neurodegeneration associated with neuroinflammation.¹⁰ Western medicine has revealed many genetic, cellular, and molecular processes that characterize AD such as protein aggregation and inflammation.¹¹ During the progression of AD, neurons from different parts of the brain are destroyed, including those areas that enable basic bodily functions like walking and swallowing.⁹ Several studies report on the phytochemicals that have been clinically proven with significant anti-AD potentials.⁷

Multiple Sclerosis

Multiple Sclerosis (MS) is a complex and heterogeneous condition from the immunologic, neuropathological and clinical point of view, as well as the way it responds to different therapies.^{12,13} This chronic complex neurodegenerative condition that targets the central nervous system (CNS) and is generally believed to be autoimmune in nature.¹⁴ It is characterized by demyelination in the CNS and leads to inability of individuals.¹⁵ MS begins in young adulthood and is more common in females and affects approximately 2.5 million people worldwide.^{16,17}

It has been stated that the etiology of MS is still unknown.^{18–20} However, this is not quite correct according to Dobson and Giovannoni.²¹ Genetic predispositions combined with environmental influences play an important role in its pathogenesis.¹⁸ Also Epstein–Barr virus, sunshine (UVB), smoking and vitamin D, combined with an individual's genetic background, play important roles in the condition's development.²² As consequence the patient develops physical, neurocognitive and psychological symptoms and deficits.²³ According to Cree, Hollenbach, Bove, et al., long-term worsening is common in patients with Recurrent Remittent MS and is largely independent of relapses or new lesion formation detected by brain MRI.²⁴ In addition, neurocognitive deterioration is related to emotional problems, in particular, depression.²⁵

These conditions serve as concrete examples of neurologic and neuro-immune conditions that affect the nervous system. The consequences are translated in physical, psychological and neurocognitive deficits that significantly affect patients and their families. In facing the reality of their complexity, the limitations of current treatments and the emerging evidence on the use of Nootropics make of them serious factors to be researched and implemented in treatment.

Nootropics

Phytochemicals as well as nootropics are vital cofactors with powerful effects on the body helping it to regain functionality.¹² In the last decade, an increasing number of herbal extracts, poly-herbal and herbo-mineral preparations and phytochemicals obtained from herbs have been studied for their neuroprotective potential in AD.²⁶ Analysis of antioxidant, anti-inflammatory, and neuroprotective phytochemicals used in various traditional medicines around the world reveal potential to ameliorate and prevent the neurodegeneration observed in AD.¹¹ This is also true in the case of many neurological conditions, where nootropics have been used. Therefore, research of phytopharmaceuticals obtained from medicinal plants of traditional origin can be beneficial.² In consequence, the natural system of medicine is exploring the remarkable benefits from the herbs used in various aspects and one of the aspects include brain function such as improving memory, improving alertness, improving intelligence, improving mental performance etc.²⁷

The term nootropic was coined by Dr. Corneliu E. Giurgea in lexical analogy to “psychotropic”, and comes from the Greek words for “mind” (noos) and “towards” (tropein).^{1,28} They are also referred to as neuroenhancers, smart drugs, memory enhancers, cognitive enhancers, and intelligence enhancers and are used in cognition deficits commonly found in patients suffering from Alzheimer's disease (AD), schizophrenia, stroke, attention

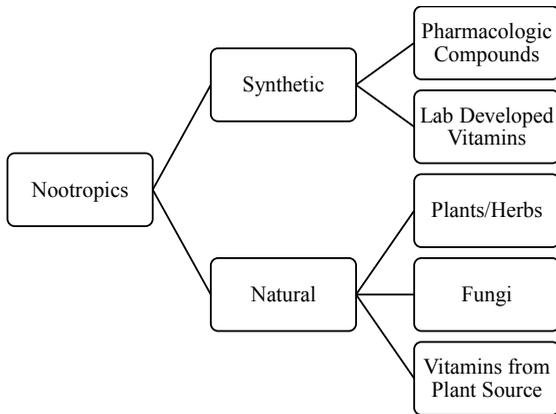


Fig. 1. Nootropic Classifications

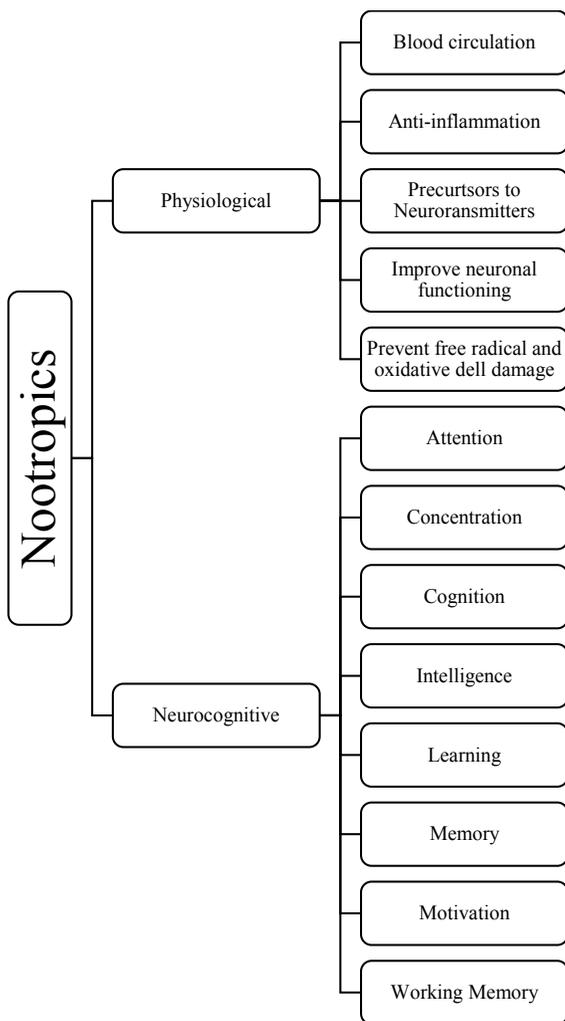


Fig. 2. Nootropic’s Physiological and Neurocognitive Enhancing Attributes

deficit hyperactivity disorder (ADHD), or aging.²⁹⁻³⁵ According to Margineanu, Dr. Giurgea detailed the definition of Nootropics, stating that they should:²⁸

1. enhance learning and memory
2. increase the resistance of learned behaviors/memories to conditions that tend to disrupt them (e.g. hypoxia)

3. protect the brain against various physical or chemical injuries (e.g. barbiturates)
4. increase the efficacy of the tonic control mechanisms of the cortex on the subcortical levels of the brain
5. lack the usual pharmacology of other psychotropic drugs (e.g. sedation, motor stimulation) and possess very few side effects and extremely low toxicity.

There are two different nootropics: a) synthetic, which are compounds created in laboratories such as Piracetam, and b) natural and herbal nootropics, such as *Ginkgo biloba* and *Panax quinquefolius* known as American Ginseng.³⁶ More specifically, within the synthetic classification, we can include not only pharmacologic compounds, but lab developed vitamins also. Natural nootropics include plants/herb, fungi and vitamins from plant/food sources (Figure 1).

Nootropics are an extensive and structurally heterogeneous class of drugs, supplements, nutraceuticals, and functional foods that enhance one or more aspects of mental function.^{27,29} Among the better known aspects (Figure 2) of mental and brain functions enhanced by nootropics reported in the literature are: a) attention, b) blood circulation, c) concentration, d) cognition, e) intelligence, f) learning, g) memory, h) motivation, and, i) working memory.^{9,27,29,37}

Nootropics site of Action

The Nootropic site of action is the brain, and they must overcome all barriers to reach brain tissue, and the blood-brain barrier (BBB) is the last critical obstacle for the permeation of drugs or substances that require CNS action.²⁹ The BBB is a delicate membrane synthesized by the endothelial cells, which makes up the inside layer of cerebral microvessels and consists of brain capillaries that support endothelial cells and are surrounded by astrocytic end-foot processes.^{7,29} It is a structure with complex cellular organization that separates the brain parenchyma from the systemic circulation.²⁹ The BBB controls the entrance of plasma components, red blood cells, and leukocytes into the CNS, while exporting the neurotoxic molecules from the brain to the blood.⁷

Purpose of Nootropics

At this point where natural compounds and neuroscience meet, the mandatory question is why use nootropics? The brain is the center of the nervous system which controls memory, thought, reason, judgment, consciousness and emotion, and supporting its health is vital to ensure successful regulation and coordination of body activities.^{27,38} Proper brain functions are essential in the therapeutic approach and treatment of both neurocognitive and mental health conditions. Cognitive enhancers can help the brain work properly.³⁸ Therefore, the implementation of nootropics as coadjutants in pro-

moting the protection of the brain and nervous system should be taken into account.

Neurodegeneration is a process involved in both neuropathological conditions and brain ageing.³⁹ On the other hand, neuroprotection refers to the strategies and relative mechanisms able to struggle down the Central Nervous System (CNS) against neuronal damage caused by neuropsychiatric and neurodegenerative disorders such as Alzheimer's disease, anxiety, cerebrovascular impairment, seizures, and Parkinson's disease, among others.⁴⁰ However, treatment of these disorders with prolonged administration of synthetic drugs will lead to severe side effects.⁴⁰ Therefore, in terms of integrative healthcare, it is imperative to move toward an approach that not only treats, but nourishes the individual's organism in order to improve neurocognitive, emotional and physical functionality.

The therapeutic effect of nootropics is based on positive affection of metabolic pathways in brain tissue (improved utilization of nutrients and mediators) and their impact manifests after some time of administration.²⁹ They are neuroprotective or extremely nontoxic and act through: a) increasing circulation to the brain, b) providing precursors to neurotransmitters, c) improving neuron function, d) preventing free radical and oxidative damage to brain cells, and e) providing usable energy to the brain and among others.²⁷ Nootropics improve memory and learning by acting as Ca-channel blockers, acetylcholinesterase inhibitors (AChEI), glycine antagonists, antioxidants, serotonergic, dopaminergic, and glutamic acid receptors antagonists, at the time they exhibit neuroprotective potentials by decreasing the burden of A β accumulation, apoptosis, synaptic dysfunction, inflammation and oxidative stress.⁹

Evidence on the Usefulness of Nootropics

In an evidence-based healthcare system the different therapeutics require scrutinized evidence on its effectiveness. Therefore, we ask, is there evidence on the usefulness of natural or non-chemical Nootropics? Within the natural nootropics division there are plants/herb, fungi and vitamins from plant/food sources. Vitamins are organic compounds that are characterized by high levels of potency, so they are only required in very small amounts.⁴¹ The B vitamins, also known as B Complex perform a wide array of important functions throughout the body, like helping to convert food into energy and maintain the immune system, healthy skin, blood cells, the brain, and the nervous system.⁴² B Vitamins are vital in cognitive function, however, vitamins which have a significant influence in brain function include: a) Thiamine (B₁), b) Cobalamin (Cyanocobalamine/Methylcobalamine, B₁₂), c) Niacinamide (B₃), d) Folic acid, and e) Choline.²⁷ In addition several epidemiological studies have exposed that blood concentrations of vita-

mins B₆, B₁₂, and folic acid are linked to people's performance on tests of memory and abstract thinking.⁴³

On the other hand, *Hericium Erinaceus* (HE) also known as Yamabushitake or Lion's Mane is an edible fungus abundant in bioactive compounds that include β -glucan polysaccharides, hericenones and erinacine terpenoids, isoindolinones, sterols, and myconutrients, which potentially have neuroprotective and neuroregenerative properties.^{44,45}

According to Jiang, Wang, Sun, et al. the functions of HE on the nervous system are divided into two types: a) HE can regulate the growth and development of the neurons and accessory structures and b) it can coordinate the functions of neurons which are associated with the complex neurodegeneration diseases.⁴⁶ On a research conducted by Ratto, Corana, Mannucci, et al., two-month oral supplementation with HE was found to reverse the age-decline of recognition memory in mice.⁴⁷ Proliferating cell nuclear antigen (PCNA) and doublecortin (DCX) immunohistochemistry in the hippocampus and cerebellum in treated mice supported a positive effect of an HE on neurogenesis in frail mice. Vigna, Morelli, Agnell, et al., assessed whether a treatment with HE improved depression, anxiety, sleep, and binge eating disorders after 8 weeks of supplementation in subjects affected by overweight or obesity under a low calorie diet regimen.⁴⁴ They found out that HE promoted an improvement in mood disorders of a depressive-anxious nature and of the quality of nocturnal rest.

Finally, there is a plant widely used and researched for its uses in cognitive improvement, named *Ginkgo biloba* (GB). This plant contains bilobalide and ginkgolide and has demonstrated antioxidant and vasoactive properties as well as clinical benefits in several conditions such as epilepsy, ischemia, and peripheral nerve damage.^{7,48} A meta-analysis of seven randomized controlled trials that consisted of 2,684 patients with Alzheimer- or vascular type dementia indicated that standard measures of overall cognition and activities of daily living improved in those who received *Ginkgo biloba* extract at 240 mg per day, whereas a daily dosage of 120 mg had no effect.⁴⁹

As it can be appreciated, Nootropics from plant, vitamin and fungi sources represent a feasible coadjuvant supplementation in the treatment of neurocognitive conditions. They will serve as functional agents as well precursors that will promote functionality and neuroprotection.

Conclusion

Natural products in general and medicinal plants in particular, are considered an important source of new chemical substances with potential therapeutic efficacy.³⁷ A number of nootropics are synthetic analogues of physiological compounds like Acetylcholine (ACh), pyridoxine (B₆), GABA, or coenzyme Q₁₀, while others are natural compounds (e.g., vinpocetine), and finally there

are other cerebral-active compounds such as nimodipine, pentoxifylline.²⁹ These examples of nootropics open the door for new research, clinical implementation and promotion of integrative health especially in cognitive neuroscience by implementing products of natural sources. This is particularly important in order to identify side-effects, drug-herb interactions, proper posology and synergic actions that may prove to improve neurocognitive functioning and health improvement.

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