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Efficacy and Effectiveness of Nootropics vs Prescription Stimulants on Academic Performance in College Students-A Scoping Review

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ABSTRACT

Background: Prescription stimulants are commonly referred to as "smart drugs" and are misused by many college students with hopes of improving academic performance. Other non- stimulants, such as nootropics, have been studied using animal models and may provide similar cognitive-enhancing properties as prescription stimulants. However, significant literature gaps exist regarding their overall efficacy and effectiveness.

Objectives:

(1) To explore and map the range of evidence on the efficacy and effectiveness of nootropics compared to prescription stimulants for improving focus and working memory in college-aged students,

(2) to determine the mechanisms of action of both nootropics and prescription amphetamines.

Methods: This review followed the Joanna Briggs Institute (JBI) recommendations for conducting scoping reviews published in the JBI Manual for Evidence Synthesis. A database search from December 1983 to September 2022 was performed in the Cochrane Library, PubMed, and Google Scholar. Potential articles were identified using index terms and keywords from their titles, abstracts, and full texts.

Results: After 714 articles were excluded for not meeting the pre-determined inclusion criteria, 74 articles were reviewed for potential inclusion. After the final analysis, 42 articles were included in this review.

Conclusion: Studies exploring the efficacy and effectiveness of nootropics mainly included healthy older participants, lacking robust human study cohorts and long-term follow-up. The potential deleterious health effects of prescription stimulants used by college students continue to be an unsolved problem. Hence, the results of empirical testing of certain nootropics to improve cognition would be particularly relevant to college-aged students.

Keywords: Ginkgo Biloba; Rhodiola Rosea; College Students; Abuse; Focus; Working Memory

Introduction

Nootropics are substances used to enhance mental and academic performance. Since 2007 there has been an estimated 40% increase in the number of prescription stimulants used to treat Attention Deficit Hyperactivity Disorder (ADD) or Attention Hyperactivity Disorder (ADHD) in children and young adults ages 4 to 17.1 Furthermore, in 2011, an estimated 50 million prescription stimulants were written to treat ADD/ADHD in U.S. children [1]. Associated with this rising trend in prescription stimulants are the demanding academic standards and rigors of gaining admittance into tier one universities and then sustaining high academic performance under high demands and workloads [1,2]. We will discuss the risks associated

with the growing use of such drugs to meet these demands, and we will explore whether there are cognitive-enhancing nootropics that may provide safer alternatives for college-aged students while also providing similar benefits. One of the most commonly used prescription drugs is Adderall (methylphenidate), a combination of four amphetamine salts. Other widely prescribed stimulants include Dexmethylphenidate and Dextroamphetamine [1,2]. These are considered schedule II-controlled drugs, which means that while it does have an accepted medical use, it has a high potential for abuse and severe psychological and physical dependence. Hence, this places Adderall in the same category as drugs such as opioid painkillers. Adderall is often prescribed for attention deficit disorder (ADD)/ attention deficit hyperactivity disorder (ADHD), and narcolepsy. Adderall is the most prescribed drug, constituting 77% of all prescribed stimulants. Additionally, adderall is the most abused brain enhancing stimulant among college-aged students [2].

Adderall is an amphetamine that augments dopamine, serotonin, and norepinephrine levels in the brain [3]. Specifically, dopamine binds to critical receptors in the brain, while epinephrine binds to receptors in the adrenal gland. Individuals diagnosed with ADD/ADHD and other similarly interrelated cognitive disorders often suffer from what is referred to as dopamine dysfunction. Individuals lacking the normal levels of this crucial neurotransmitter may experience loss of motivation, fatigue, mood disorders, working memory problems, and difficulties supporting focus and concentration [3]. Hence, stimulants such as Adderall® and Ritalin® increase dopamine concentrations leading to improved focus, working memory, enhanced motivation, improved mood states, and sustained focus and concentration [3]. Arria, et al. [4] found that 1 in 5 college students use non-medical prescription drugs such as Adderall®, Concerta®, and Ritalin® often taken in combination with other drugs such as marijuana, cocaine, ecstasy, opiates, and alcohol. College-aged students taking non-medical stimulants have hopes of boosting their intelligence, thereby giving them an academic performance advantage. However, without a proper evaluation, diagnosis, and supervision of a licensed medical provider, individuals who take these highly potent stimulants may experience serious health issues and side effects such as cardiac irregularities, paranoia, psychological/physiological dependence, and addiction [4].

Drugs such as Adderall® are commonly referred to as «smart drugs» by college-aged students. They are perceived as productive for improving academic performance and providing a competitive edge [5]. Many students consider such drugs necessary to succeed within a highly competitive academic ecosystem. Thus, many students will find ways to take these drugs when studying for exams to cultivate their working memory and performance. Although the efficacy and effectiveness of such stimulants may lead to acute improvements in working memory and concentration, their long-term use could lead to psychological and physical dependence [5]. Physical and psychological addiction to amphetamines, such as Adderall®, is primarily linked to the increased synthesis and secretion of dopamine, serotonin, and norepinephrine. These chemical messengers comprise roughly three of the seven critical neurotransmitters in the body [6]. Each one of these chemical messengers is synthesized and then secreted in the body, with the primary aim of attaching to a specific target cell. Collectively, neurotransmitters aid in regulating blood pressure, heart rate, digestion, skeletal muscle movement, mood, concentration, and working memory. Nevertheless, long-term use of these brain-stimulating drugs may lead to a broad spectrum of interrelated cardiac health disorders, such as hypertension, tachycardia, stroke, seizures, and cardiomyopathy. For example, hypertrophic cardiomyopathy is a severe condition defined as hypertrophy (thickening) of the myocardium chamber walls resulting in a reduced cardiac output (CO). CO is the volume of blood ejected from the heart's right and left ventricles. Heart impedes the flow and distribution of oxygen-rich blood to the body's periphery organs, tissues, and muscles [6].

The use and potential abuse of prescription drugs among college-aged students have profound physical and mental effects. The misuse of these prescription stimulants has triggered the creation of community advocacy groups on many college campuses with the primary aim of averting the abuse of stimulant drugs among college students [7]. For example, Kennedy, et al. [7] published an article entitled «Raising awareness about prescription and stimulant abuse on-campus community involvement projects.» They found that these types of advocacy groups have been ineffective, thus far, in preventing the high misuse of prescription stimulants on college campuses [7]. Additionally, Abelman [8] published a similar review on mitigating risks of students' use of study drugs such as Adderall® and found that numerous students still believe these types of brain-enhancing medications are necessary to keep up with the rigors and demands of the academic institutions they attend [8].

Given the potentially dangerous side effects and safety profile of synthetic stimulants such as Adderall®, there exists a need for a safer, alternative nootropic or a cocktail of nootropics that may have similar efficacy and effectiveness for improving focus, working memory, and concentration in college-aged students diagnosed with ADD/ ADHD. The need exists to explore various combinations of nootropics with similar mechanisms of action as synthetic prescription smart drugs for improving focus, working memory, and concentration. Further, if the efficacy and effectiveness are identical between nootropics and prescription stimulants, what are the differences in their safety profiles? This question, as well as others on the efficacy and effectiveness of these brain-enhancing nootropics, remains unanswered in the scientific literature and, thus, deserves further inquiry.

Nootropics commonly referred to as «smart drugs» or «cognitive enhancers (CEs),» are natural brain-enhancing substances that provide safer and potentially cognitive health-enhancing effects that can be used in place of prescription stimulants, such as Adderall. Nootropics are compounds, supplements, or drugs made to enhance cognitive function and are considered adaptogenic in managing stress-related disorders [9]. For example, a true nootropic can

1) Increase resistance to stress hormones (cortisol, adrenaline),

2) Improve concentration and short-term memory,

3) May protect glial cells 4 & 6 and information messengers in the brain known as neurons, and

4) Improved neuronal communication through direct electrical coupling and increased secretion of neurotransmitters in the brain [10].

The aims of this scoping review were to

1) Explore and map the range of the most recent evidence on the efficacy and effectiveness of nootropics compared to prescription amphetamines for improving focus and working memory in college-aged students, and to determine the mechanisms of action of both nootropics and prescription stimulants,

2) To understand whether there is evidence to support the use of nootropics to increase focus, concentration, and working memory in college-aged students without the potential side effects. This review defines efficacy as assessing the difference between nootropics and prescription amphetamines in a controlled laboratory. In addition, effectiveness is determined as the academic Grade Point Cumulative (GPC) of students taking nootropics compared to students taking amphetamines in a real-world environment.

Our primary question for this scoping review was (1) is there sufficient empirical evidence regarding the efficacy and effectiveness of nootropics for improving mental alertness, concentration, and working memory in college-aged students? Additionally, a sub-question was (2) how do the mechanisms of action of nootropics differ from those of commonly prescribed amphetamines used to treat ADD/ADHD?. Lastly, we hypothesize that if nootropics are used over a specified period at the correct dosage (based on milligrams per kilogram of body weight), then similar efficacy and effectiveness may be achieved with safer alternatives.

Methods

This scoping review fulfills the PRISMA-ScR [11]. We followed the Joanna Briggs Institute (JBI) guidance for conducting scoping reviews published in the JBI Manual for Evidence Synthesis [12]. This review is not registered in the JBI database for reviews and implementation. However, this review can be acquired on request from the corresponding author.

Inclusion Criteria

Primary, secondary, and tertiary articles in English were eligible for inclusion. Peer-reviewed articles and grey literature that focused on "interventions," such as stimulants and nootropics used to improve mental alertness, concentration, and working memory, were eligible for inclusion. Articles that focused on "phenomena of interest" concerning the mechanisms of action of nootropics compared to commonly prescribed stimulants used to treat ADD/ADHD were eligible for inclusion. Lastly, articles that provided sufficient evidence to support the use of nootropics for improving mental alertness, concentration, and working memory in college-age students were eligible for consideration.

Search Strategy & Screening

The authors (CO, SL) performed a three-step search strategy according to the JBI Methodology for Scoping Reviews [11,12]. We conducted an initial title and abstract limited database search using the Cochrane Library, PubMed, and Google Scholar related to the topic, primary review question, and objectives. For the second database search, we used the index terms and keywords from the articles we located during the initial search. Lastly, we reviewed other pertinent reference lists of the eligible full-text articles. For our first search in the Cochrane Library, we performed an advanced all-text search for articles published from 1983 to 2022 related to the primary review question, which was entered as (Rhodiola Rosea) OR (Ginkgo Biloba) OR (Amphetamines) AND (College Students), which produced 63 Cochrane Reviews, 13 Cochrane protocols, 1094 trials, and two clinical answers. There were no registered Cochrane protocols related to our topic or question and no clinical answers. Most protocols and clinical answers the search yielded were related to dietary interventions and dementia and focused on the efficacy of Ginkgo Biloba and antioxidants in treating schizophrenia and bipolar disorder.

For our first abstract search in PubMed, we included the following article types: books and documents, clinical trials, meta-analyses, randomized controlled trials, reviews, systematic reviews, and Google Scholar articles published between 31 December 1983 to 12 September 2022. We used critical terms as descriptors for all database searches performed and connected them with Boolean logic operators. The first search terms entered in the advanced search builder in PubMed relevant to this review topic were (Efficacy) OR (Effectiveness) AND (Rhodiola Rosea) OR (Ginkgo Biloba) OR (Stimulants) AND (College Students), which produced 76 articles; 47 were retrieved for further analysis of the text words used in the title and the index terms that described the articles. For the second search in PubMed, we entered (Efficacy) OR (Effectiveness) AND (Amphetamines) OR (Academic Performance) AND (College Students), which generated 257 articles related to the scoping topic; 24 were retrieved for further analysis of text terms and index terms. Our third search in PubMed was related to the primary review question, which was entered into the search query as (Efficacy) OR (Effectiveness) AND (Rhodiola Rosea) OR (Ginkgo Biloba) AND (Working Memory), which produced 11 articles; 10 were retrieved for further analysis of text words and index terms. Our last search in PubMed was related to the secondary review question. For this search, we entered (Mechanisms of Action) AND (Rhodiola Rosea) OR (Ginkgo Biloba) OR (Amphetamines), which generated 1,593 potential articles; 150 were retrieved for further analysis.

Lastly, we performed our initial advanced search in Google Scholar by selecting any type of article in the search query box, which included all article types associated with the primary review question published from 1983 to 2022. The search terms and keywords were entered as (Efficacy) OR (Effectiveness) AND (Rhodiola Rosea) AND (Ginkgo Biloba) AND (Stimulants) AND (College Students), which

yielded 288 articles. Lastly, we performed an advanced search in Google Scholar related to our secondary review question, which was entered as (Mechanisms of Action) AND (Rhodiola Rosea) AND (Ginkgo Biloba) AND (Amphetamines), which generated 1,800 potential articles.

Source Selection

The authors (CO, SL) independently reviewed sources based on the review's title/topic, primary question, sub-question, and aims. However, before independently reviewing sources, we determined the source selection process by randomly retrieving 15 free full-text articles relevant to the review topic and initial working title. After screening these articles, we agreed on an eligibility criteria checklist as a team and then developed a data extraction document. Articles were then independently appraised by both authors (CO, SL) using the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses [12]. Any disagreement among the reviewers (CO, LS) was resolved by a third reviewer (RO). Research data extracted and analyzed from all articles included authors, publication date, source type, aims, methods and materials, and significant outcomes.

Results

Figure 1 illustrates the review flowchart for selecting sources. All sources were screened for eligibility based on pre-determined inclusion criteria. The records identified from the electronic database searches generated 4,565 primary, secondary, and grey literature articles. We located 23 additional records through the reference lists of the sources we assessed for potential inclusion. We removed 714 records that did not meet inclusion criteria and duplicate sources. Seventy-four articles were assessed for potential inclusion, and 42 were included for review.

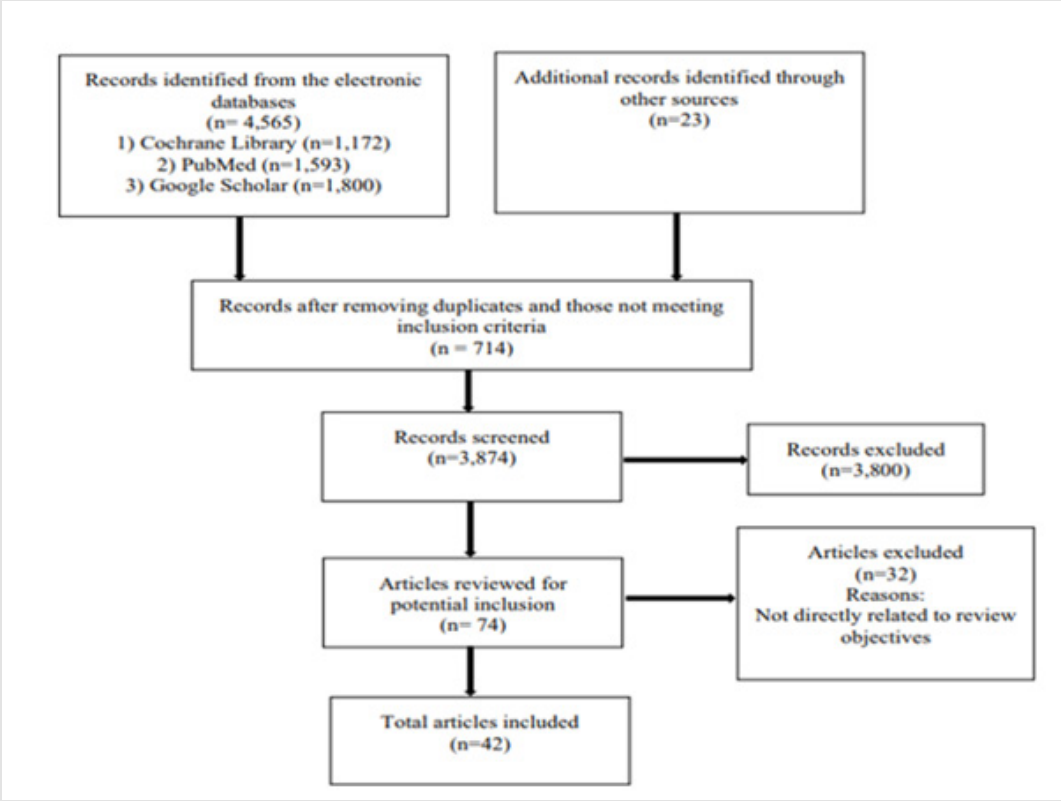

Figure 1: Literature flowchart.

Discussion

A growing market and demand for nootropics continue to exist [13]. For example, Crawford, et al. [14] predicted that the nootropics market would soon proliferate into a «multibillion-dollar business» due to the increasing demand for cognitive-enhancing supplements. However, research on the effectiveness of nootropics in college-aged students are limited in the scientific literature, with a greater emphasis on the neuroprotective advantages of nootropics. Although the neuroprotective benefits of nootropics are widely elucidated in the literature, additional research is needed with a primary focus on the potentially cognitive-enhancing properties of nootropic supplements. The adaptogenic properties of nootropics have been demonstrated to be particularly effective in treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's [15].

Potential Benefits of Rhodiola Rosea

1) Rhodiola Rosea (R.R.) is a nootropic comprising roughly 140 active ingredients. The two most potent ingredients in R.R. are rosavin and salidroside [16]. One of the essential active compounds in R.R. is salidroside, a glucoside of tyrosol, which may deliver powerful central nervous system (CNS) and neuroprotective effects, often leading to reduced symptoms of depression and anxiety [17]. Specifically, the salidroside found in R.R. may play a suggestive role in regulating pertinent stress response systems such as the reduction of free radicals,

2) The regulation of the hypothalamic-pituitary-adrenal axis (HPA),

3) Enhanced neural transmission, and regeneration, and

4) Management of the cholinergic response [16,17].

Furthermore, R.R. may assist in activating the adrenal medulla to secrete hormones, such as dopamine, and serotonin, in the CNS and sympathetic nervous system (SNS), regulating mood and other cognitive processes. Finally, although nootropics are considered to have adaptogen properties, they have not been extensively studied in humans [18]. Collectively, R.R. may activate and heighten neurotransmission responses, thus, improving working memory. For example, R.R. may enhance the effects of neurotransmitters in the brain by entering the blood-brain barrier to precursors of dopamine (DA) and serotonin (5-HT) [19]. Additionally, salidroside has been proposed to have high medical efficacy and low toxicity to the central nervous system (CNS), with marginal side effects [17]. Salidroside may also benefit individuals diagnosed with psychiatric disorders and bodily fatigue. Lastly, long-term use of R.R. may also regulate symptoms of depression and fatigue [19]. The possible actions of R.R., when given in small and moderate doses, stimulate norepinephrine, dopamine, serotonin, and nicotinic cholinergic effects in the Central Nervous System (CNS) [19,20]. Collectively, the effects begin from the brain stem affecting the cerebral cortex, which regulates cognitive functions (attention, learning, memory), and the limbic system pathways responsible for regulating the hippocampus, amygdala, and hypothalamus, all of which are responsible for regulating emotion, working memory, vigilance, pleasure, satiety, mental drive, and pleasure.19 Nonetheless, more longitudinal studies are needed using large human study cohorts to fully explain the potential benefits of R.R., especially in college-aged students.

Rhodiola Rosea may produce less harmful physiological effects than synthetic-derived stimulants based on extensive toxicological studies conducted on the plant species R. rosea. For example, R.R. might interact with specific diabetes, hypertensive, and immunosuppressant drugs [19]. Nonetheless, Brown, et al. [19] found that R.R. presents minimal side effects, and individuals regularly taking R.R. reported improvements in their mood, energy level, and mental clarity [15,19,20]. Rhodiola Rosea may also have positive effects on the prefrontal and frontal cortex of the brain, if given in the proper dose and frequency [19]. According to Brown, et al. [19] «Approximately 94 percent of all human studies and 51 percent of all animal studies conducted on plants in the genus Rhodiola are on the species R. rosea. Only R. rosea has passed extensive toxicological studies and has been certified safe for animals and humans [19].» However, many of these studies lacked long-term follow-up, included small study cohorts, and have used only animal models.

The neurophysiological actions of R.R. may directly affect emotional tone by enhancing neurotransmitter monoamine levels (N.E., DA, 5-HT) in nerve tracts in the amygdala, hippocampus, hypothalamus, and midbrain [19,20]. Anecdotal evidence suggests that all are involved in regulating mood, anxiety, and emotions. Other potential benefits of R.R. include the prevention of high-altitude pulmonary edema (HAPE). Rhodiola Rosea has been broadly used by individuals working and sojourning at high altitudes exceeding 10,000 feet in sub-arctic regions [21]. Further, R.R. is a commonly sourced nootropic in traditional medical systems throughout Asia and Europe. Collectively, anecdotal evidence suggests that R.R. may ameliorate the functioning of the nervous system, reduce depressive symptoms, augment working memory, lessens fatigue, and diminishes high altitude sickness [19-21]. Nonetheless, many of these studies were conducted using animal models and thus deserve further inquiry regarding their effects on humans. Zhong, et al. [17] conducted clinical safety trials on R.R. using Sprague Dawley (S.D.) rats. They found that the critical composite, salidroside is safe and does not result in maternal or embryonic toxicity. Additionally, S.D. rats had no teratogenic effects when they were given R.R. at doses of 0.5 grams/kilogram (g/kg), 0.25 g/kg, and 0.125 g/kg [17]. Zhong and colleagues also found that the results of the Ames test, reverse mutation assay, chromosomal aberrations assay, and mouse micronucleus assay showed that salidroside is not genotoxic at a clinical dose (e.g.,150 mg/60 kg/day) for humans [17]. Lastly, the lack of adverse effects during pre-clinical and clinical trials indicates that salidroside may show promise but warrants additional human clinical trials to support these findings [17].

Bioactive Composites of Rhodiola Rosea

Rhodiola Rosea may be an effective facilitator of transmitters in the brain known as neurotransmitters. Rhodiola Rosea has similar mechanistic features of prescribed stimulants used to increase neurotransmission and the neurotransmitters' levels. Together, they heighten communication between neurons via electrical signals known as action potentials. These action potentials reach the axon terminal proliferating into the neuron, preventing brain chemicals such as dopamine, serotonin, and acetylcholine from reuptake. By preventing the reuptake of these chemicals, they remain in the synapse for more extended periods, which allows sustainment of an individual's concentration, and focus and may result in feelings of euphoria [22]. The adaptogenic properties of R.R., cardiopulmonary protective effects, and elicitation of the CNS are attributed to R.R.'s ability to activate the levels and activity of monoamines and opioid peptides such as beta-endorphins [21]. Although the biological mechanisms of R.R. may exhibit similar biological pathways as prescription stimulants, there exist significant gaps in the literature

regarding their efficacy and effectiveness in improving working memory, focus, and concentration.

The central bioactive compound in R.R. is 1% salidroside, which has essential pharmacokinetic effects. The pharmacokinetics of a drug and its constituent composites reveals how drug compounds are absorbed in the body [17]. For example, Zhuang, et al. [23] found that the plasma concentration of salidroside dissipated precipitously at doses ranging from 7.15, 15, and 30 mg/kg. In the final analysis, salidroside presented a short half-life of roughly 60 minutes. Moreover, an estimated 54% of the salidroside was excreted from the rats, implying that metabolism plays an essential role in promptly eliminating salidroside [23]. Hence, the importance of dosing relative to body weight (mg/kg/B.W.) should be considered when exploring the effects of this bioactive compound found in R.R. Nonetheless, the bioactive compound salidroside may afford some protection to the cardiovascular system, is operative in ameliorating depression, and may deliver a prophylactic effect in averting traumatic brain injury (TBI). However, most of these studies were performed on animal models and lacked robust empirical studies on humans.

Biological Mechanisms for Rhodiola Rosea

The scientific interest in exploring the effects of salidroside, the most bioactive ingredient in R.R., on cognition and other medically relevant health disorders has significantly increased from 1992 to 2017 [17]. For instance, over 25 years, 299 publications relevant to the physiological and psychological effects and mechanisms of action of salidroside have been published [17]. However, most studies on the precise mechanism of action have been conducted on animals [19,2]. Nonetheless, several studies have elucidated the neurophysiological effects of R.R. and the potential benefits of R.R.s adaptogen features for improving cognition and regulating an array of pathophysiological disorders. Kelley, et al. [21] studied the effects of monoamine levels in rats. They found that R.R. reduced the activity of the enzymes, such as Monoamine oxidases (MAO)-A and MAO-B, two isoenzymes genetically prevalent in all mammals. Specific substrates for MAO include central brain neurotransmitters such as dopamine, norepinephrine, epinephrine, and serotonin. Some mammals are deficient in various phenotypes of MOA due to either environmental or genetic influences, which can lead to an assortment of neurodegenerative pathologies, such as ADHD, dementia, and Parkinson's disease. The clinical trial performed by Kelly [21] included the oral administration of a water extract of R.R. to mice for ten consecutive days. After ten days, he found that the biogenic monoamines were modulated in the cerebral cortex, brain stem, and hypothalamus. In other words, R.R. helps transport and support levels of the biogenic amines, norepinephrine, histamine, dopamine, and serotonin, all considered vital neurotransmitters in the brain [21]. More specifically, kelly [21] found a three-fold increase in the concentration of dopamine and norepinephrine in the hypothalamus and a trend toward reduced serotonin levels responsible for managing hormones and supporting homeostatic levels in the body [21].

Impact of Ginkgo Biloba (G.B.) on Health

Ginkgo Biloba (G.B.), also referred to as maidenhair, is a unique tree comprised of one species in the genus known as Ginkgo. The maidenhair is a million-year-old tree grown for centuries in Southeast Asia and is well known for its neuroprotective uses [9,24]. Ginkgo biloba leaves encompass roughly 24% flavone glycosides, 6% terpene lactones, and 0.8% to 3% bilobalide and Ginkgolide B extracts [25]. Several proposed yet unsubstantiated benefits on large human study cohorts of the Ginkgo extracts are

1) Improved microcirculation (blood flow),
2) Effective free radical scavengers within cells,
3) Regulation of neurotransmitters, and
4) Deliver potent neuroprotective effects in the brain [25].

The critical bioactive composite of G.B. extract is EGb761®, extracted from the maidenhair tree leaves. The EGb 761® extract is regarded as a «living fossil» and recognized as Ginkgophyta, a division of gymnosperms plants identified as Ginkgoales [24,26]. The extracts from the Ginkgo tree are used in traditional Chinese medicine, mainly as a food source that Chinese monks have grown and cultivated over the recent millennia [15]. Ginkgo Biloba has been studied to deliver neuroprotective effects and treatment of Alzheimer's and Parkinson's Disease [27]. As previously noted, the essential bioactive composite of G.B. is the EGb761® extract, made up of terpenes and flavonoids. Droy-Lefaix [28] explored the effect of the antioxidant action of Ginkgo biloba extract EGb761® on aging and oxidative stress. He discovered that EGb761® extract might improve the functionality of the electron transport chain in the oxidative powerhouse of the cell known as the mitochondria. Further, EGb761® may aid in the degradation of peroxyl free radicals and superoxide anions, improve neurotransmitters' absorption, ameliorate ischemic reperfusion episodes, and inhibit apoptosis (cell death) [28].

Impact of Ginkgo Biloba (G.B.) on Cognition

The ginkgo extract EGb 761® may also improve cognitive processing ability. Beck, et al. [29] conducted an 8-week randomized, double-blind, placebo-controlled trial of G.B. extract EGb 761® on cognitive control functions, the mental activity of the prefrontal cortex, and stress reactivity in elderly adults with qualitative memory impairment. Seventy-five participants volunteered for this study between the ages of 50 to 65. Participants had to score average or slightly below average on the I.Q. scale of ≥ 85 to ≤ 115 and had subjective memory impairment. The participants were randomly assigned to either placebo (n=32) or treatment (EGb761) group (n=43). The treatment group received 240 mg of EGb761® daily for 56 days [29]. Beck et al. [29] found that participants in the treatment group improved cognitive flexibility with no changes in brain activation, improved cognitive processing efficiency, and experienced mild prefrontal dopaminergic enhancement. Nonetheless, the authors noted that improvements in dopaminergic function should be

confirmed through more human trials that directly assess the effects of EGb761® on dopaminergic systems [29].

In a similar study, Kehr, et al. [30] examined the effects of the G.B. leaf extract EGb761® on dopamine, noradrenaline, serotonin, and acetylcholine levels in a rat's medial prefrontal cortex. Rats were given 100 or 300 mg/kg subacute oral drops of EGb761® or the flavonoid fraction (24% of the whole extract) once daily for 14 consecutive days. The results revealed a significant dose-response increase in dopamine levels in the rat's medial prefrontal cortex. Also, recurring administration of EGb761® extract induced a significant yet limited upsurge in norepinephrine levels; however, serotonin levels were not affected [30]. In vitro studies on animal models suggest that G.B. may offer cognitive-enhancing effects. For example, Stough, et al. [31] explored the potential effects of G.B. leaf extract on memory and cognition in 61 healthy adults ages 18 to 40. Study participants had no history of traumatic brain injury and were not taking prescription medications or over-the-counter dietary supplements. Participants were given either a placebo or 120 mg of G.B. (treatment) in tablet form for 30 consecutive days. The dependent variables studied were

1) Measured attention,
2) Working and short-term memory,
3) Verbal learning,
4) Memory association,
5) Executive processing,
6) Planning and problem-solving,
7) Information processing speed, and
8) Motor responsiveness and decision-making. The author's found that cognitive clarity and self-reported improvements in memory and attention significantly improved in the G.B. treatment group ($F= 14.7$, $p<0.001$) compared to the placebo group [31].

Ginkgo Biloba (G.B.): Postulated Mechanisms of Action

The critical enzyme responsible for removing key neurotransmitters in the brain, such as dopamine, norepinephrine, and serotonin, is Monoamine Oxidase (MAO). Monoamine Oxidases A and B are specific isoenzymes responsible for the degradation of biogenetic amines epinephrine, dopamine, and catecholamines. MAO-A and MAB-B are found throughout the brain and on the outer membrane of the mitochondria. Monoamine oxidase inhibitors (MAOIs) are prescribed to treat depression. Further, MAOIs inhibit the degradation of biogenetic amines in the brain, thus increasing their availability for uptake by the brain while offering some protective features to neuroglial cells, which are critical to the brain's electrical signaling processes [32]. Ginkgo biloba has been shown to inhibit MAOs. For example, White, et al. [33] found that rats administered dried G.B. leave extract showed similar drops in MAO-A and MAO-B concentrations, which may partially explain the increases in monoamine concentrations. This pathway should be studied more, as studies are conflicting regarding the biological pathway contributing to dopamine increase in the brain, which may be due to something other than MAO inhibition [34]. Additionally, two other studies on mice concluded that MAO was also inhibited. These results are linked to Kaempferol, a flavonoid shown to be an MAO inhibitor [34-36].

Although Ginkgo Biloba may enhance brain cognition by strengthening key signaling pathways between neurons through the inhibition of MAO and potentially via the Vesicular Monoamine Transporter 2 (VMAT-2), the precise way in which the VMAT-2 enhances cognition is still elusive [37]. Nonetheless, the VMAT-2 is an essential presynaptic protein responsible for transporting monoamines (dopamine, serotonin) from the cell cytosol into the synaptic vesicles to be released and used [37]. The effects of G.B. on the VMAT-2 transporter show similar biological pathways as prescription stimulants known to treat ADD and ADHD. Although the biological pathways of MAO may be analogous to prescription stimulants, empirical studies are needed to understand their similarities in modes of action.

Biological Mechanisms of Prescription Stimulants

As previously noted, Adderall (methylphenidate) comprises mixed amphetamine salts and dextroamphetamine in a 3:1 ratio [38]. For example, the molecular formula for Adderall® is transcribed as C9H13N, consisting of a benzene aromatic ring bonded with an amine side group. Once Adderall® is catabolized, it passes from the presynaptic barrier to the synaptic vesicles, where it is stored. The primary protein carrier known as the dopamine transporter (DAT) helps remove dopamine molecules from the extracellular and cytosolic spaces aiding in the number of dopamine molecules secreted from the synaptic vesicles [3,39]. The increased dopamine secretion is a necessary precursor for specific neurotransmitters known as epinephrine (adrenaline) and norepinephrine (noradrenaline) [40]. Dopamine is an essential neuromodulator molecule, which includes roughly 80% of all catecholamines in the brain [40]. Hence, dopamine is considered vital for enhancing motivational salience in individuals who require increased motivation, concentration, and focus while completing a task or series of complex tasks [40].

From a broad perspective, prescription stimulants' critical mechanisms of action are to block the reuptake of norepinephrine, serotonin, and dopamine into the presynaptic neuron and thus increase the release of monoamines into the synaptic cleft. The neurophysiological effects of many prescription stimulants, such as Ritalin® and Adderall®, will precipitously dissipate once the chemical compounds are absorbed in the gastrointestinal tract, with peak concentration reached within three to four hours [41]. Although the brain is more metabolically active on stimulant drugs, they pose short- and long-term addictive health risks [41]. The prescription amphetamines commonly used to support focus and concentration in college students and adults stimulate the production of brain molecules known as monoamines leading to an increased risk of long-term addiction [41]. Long-term addiction is primarily attributed to repeated cumulative inductions of euphoria and the cumulative secretions of monoamines [41]. Subsequently, an array of side effects

exists, such as increased resting heart and blood pressure, psychosis, neurosis, nausea, weight loss, dry mouth, and loss of appetite [41]. The physiological side effects, such as high resting heart rate and the potential for long-term addiction, are partially explained by the deactivation of epinephrine receptors and adrenaline over time [41]. In other words, these receptors become saturated with brain chemicals over time through the constant flux of amphetamines binding to their receptors. Nonetheless, prescription drugs continue attracting healthy, college-aged students not diagnosed with ADD or ADHD to misuse amphetamines to enhance their focus and concentration, likely attributed to high academic demands and high academic workloads.

Impact of Prescription Stimulants on College Students

The use of prescription stimulant drugs, such as Ritalin® and Adderall®, has significantly increased in recent years [4]. For example, the nonmedical use of prescription stimulants is considered more prevalent among sub-groups of U.S. college students and universities. For example, McCabe, et al. [42] studied healthy Caucasian white college male students ages 18 to 25 with reported overall low-grade point averages [42]. Based on the results of the multivariate analysis, he found that non-prescription use of Adderall was reportedly higher amongst white male and female college students who were members of fraternities and sororities [2]. Additionally, rates of prescription stimulant use were higher at universities found in the northeastern region of the U.S. and among universities with more competitive admission standards [2]. In particular, the academic rigors of schools with higher academic expectations may lead students to turn toward taking prescription stimulants [2].

As previously noted, the potential health risks associated with taking highly potent and addictive amphetamines like Adderall® may pose significant long-term physiological and psychological health risks. For example, Abelman et al. [8] found that prescription stimulant drugs used to enhance cognition may produce symptoms of malnutrition, high blood pressure, and feelings of anxiety, and may further potentiate the likelihood of experiencing a stroke «[8]. Further, «Pharmaceutical companies and addiction associations describe them as highly addicting substances with the potential to cause serious cardiovascular issues such as sudden cardiac death, stroke, seizures, and internal organ dysfunction, particularly of the kidneys and liver. Potential long-term psychological impairments may include psychosis, paranoia, anxiety, and depression in some individuals [8]».

Conclusions and Implications

Based on the potential long-term harmful health effects of prescription stimulant drugs used by college-aged students with and without diagnosed ADD and ADHD, there is a need for cognitive-enhancing drugs that offer safer pharmacokinetic profiles. Although we found specific nootropics that display similar mechanisms of action as prescription stimulants such as Adderall® and Ritalin®, the literature is scant on clinical trials using these nootropics on humans, especially in large, longitudinal study cohorts. Additionally, many clinical trials using these nootropics have been studied on animals and lack robust human clinical trials to support their efficacy and effectiveness. Thus, we refuted our initial hypothesis due to a lack of clinical evidence; however, moderate evidence exists that nootropics, such as R.R. and G.B., might serve as safer alternatives. Nonetheless, longitudinal studies using younger healthy human participants should be considered in the future, and these studies should further be replicated in heterogeneous human populations.

We found that most studies testing the efficacy and effectiveness of nootropics have been primarily conducted on healthy older participants. Therefore, more longitudinal clinical studies using human participants should be considered, especially from a longitudinal perspective. These studies should further examine the safety profiles of certain nootropics and their long-term effects. Nootropics that have been explored extensively on animal models should advance to human clinical trials, and investigators should consider exploring their effects on college-aged students diagnosed with ADD/ADHD. Lastly, and perhaps most importantly, further empirical studies are needed regarding nootropics' long-term efficacy and effectiveness in enhancing cognition, especially in college-aged students seeking safer cognitive enhancing alternatives.

Disclaimer

The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of William Beaumont Army Medical Center, the Defense Health Agency, the US Army Medical Department, the US Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, the Department of Defense or the US Government.

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Author Contributions

CO and SL conceived the concept of writing this review and performed the first literature search and wrote the first draft of this review article. RO performed extensive revisions to all major sections and developed all subsections of the Methods, Results, and the Discussion. SL and CO performed additional literature searches and transcribed the Introduction section of the review. Lastly, RO performed an extensive review and re-write of the Introduction section of this review.

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