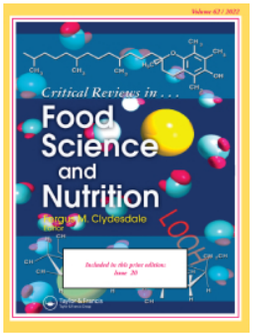

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REVIEW

Plant-derived nootropics and human cognition: A systematic review

Cristina Lorca[a,b,c], María Mulet[b], Catalina Arévalo-Caro[b], M. Ángeles Sanchez[a], Ainhoa Perez[a], María Perrino[a], Anna Bach-Faig[d,e], Alicia Aguilar-Martínez[d], Elisabet Vilella[f,g,h], Xavier Gallart-Palau[b,c,f,h*] and Aida Serra[a,b,c]

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ABSTRACT

Substances with modulatory capabilities on certain aspects of human cognition have been revered as nootropics from the dawn of time. The plant kingdom provides most of the currently available nootropics of natural origin. Here, in this systematic review, we aim to provide state-of-the-art information regarding proven and unproven effects of plant-derived nootropics (PDNs) on human cognition in conditions of health and disease. Six independent searches, one for each neurocognitive domain (NCD), were performed in parallel using three independent scientific library databases: PubMed, Cochrane and Scopus. Only scientific studies and systematic reviews with humans published between January 2000 and November 2021 were reviewed, and 256 papers were included. *Ginkgo biloba* was the most relevant nootropic regarding perceptual and motor functions. *Bacopa monnieri* improves language, learning and memory. *Withania somnifera* (Ashwagandha) modulates anxiety and social-related cognitions. Caffeine enhances attention and executive functions. Together, the results from the compiled studies highlight the nootropic effects and the inconsistencies regarding PDNs that require further research.

KEYWORDS

Plant nootropics; cognitive enhancers; learning; memory; anxiety; motor skills; perceptual skills; cognitive decay; natural compounds; herbal extracts; phytotherapy; tinnitus; dementia; Parkinson's disease; Alzheimer's disease

Introduction

Plants and plant-derived compounds have been used to prevent illness-related conditions and promote wellbeing since the dawn of time (Petrovska 2012). Those aimed at enhancing and improving cognition, a key trait of humans that differentiates us from the rest of the living forms on Earth, represent a significant portion of the pharmacopeia available to ancient cultures and civilizations (Farooqui et al. 2018). It was thus already known in these ancient communities that improvements in cognition help humans thrive and are directly associated with better achievement in most areas of life (Agarwa et al. 2014; Kulkarni, Girish, and Kumar 2012).

A traditional medical corpus on Ayurvedic medicine that can be dated back to 6,000 BCE (Mangathayaru 2013) documents the use of "Medhya Rasayanas," a group of medicinal plants that improve memory and intelligence. Plants categorized as *Medhya Rasayanas* include Ashwagandha (*Withania somnifera* (L.) Dunal), Brahmi (*Bacopa monnieri* (L.) Pennell (Bm)) and Jyotiṣmatīr (*Celastrus paniculatus* Willd.) (Kulkarni, Girish, and Kumar 2012). Similarly, the use of natural products such as *Polygala tenuifolia* Willd. (RAPO), the fungus lion's mane (*Hericium erinaceus* (Bull.) Pers.) or the fungus Reishi (Ganoderma lucidum (Curtis) P. Karst.) in traditional Chinese medicine (TCM) to improve cognitive function and treat incipient manifestations of cognitive decline were documented in recovered manuscripts that date back to nearly 5,000 years ago (Lin et al. 2012; Tierra and Tierra 1998). The use of natural nootropics was also revered in ancient medical treatises from Arabia, Egypt and Sumeria, to mention only a few historical precedents (Al Akeel et al. 2018; Hobbs and Gardner 2013).

Substances that enhance brain and cognitive performance are known as nootropics (Onaolapo, Obelawo, and Onaolapo 2019). Although there is a wide group of molecules that fit into this rather vague category (e.g., vitamins found in foods, such as B12, which can enhance cognitive performance by ensuring proper brain metabolic function), in this paper, we exclusively focused on substances of plant-derived origins that

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could theoretically enhance certain aspects of basic brain performance beyond a state of normal cognitive functionality in conditions of health and disease. Furthermore, the structure of this systematic review was based on the effect(s) that plant-derived nootropics (PDNs) exert on each specific neurocognitive domain (NCD), as defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Sachdev et al. 2014). Certainly, these single substances and mixtures may impact more than one NCD. Therefore, each PDN was linked to the NCD on which it exerts its main scientifically proven effects, but some PDNs are also briefly detailed in the section 'Other PDNs' available in the supplementary materials. We did not include animal studies that report cognitive-enhancing effects of PDNs. Although we strongly believe that these studies are crucial to further understand the mechanisms of action of these substances on the nervous system, we also think that we must be cautious when considering any potential translation of the observed cognitive effects in animals to the highly complex human cognitive system. Similarly, we realized that a proper fit from animal studies could not be established here, since the structure of this review is based on the recently established NCDs in the DSM-5. Therefore, a review of the PDN data from animal models remained out of the scope of this systematic review.

Based on the latest DSM-5 classification, the concept of human cognition can be divided into the following six basic domains: (1) perceptual-motor functions; (2) Language; (3) learning and memory; (4) social cognition; (5) complex attention; and (6) executive functions (Sachdev et al. 2014). Each of these basic domains includes several subdomains, which together facilitate the diagnosis, research, and evaluation of human cognition and cognitive decline associated with aging or neurodegeneration (Sachdev et al. 2014). Due to the breadth of the question regarding the effectiveness of nootropics in this systematic review, six individual searches, one for each NCD, were conducted in the following databases: PubMed, Cochrane and Scopus. The search details as well as the inclusion and exclusion criteria are detailed in the 'Systematic search strategy' section of the supplementary materials.

As illustrated in Figure 1, a total of 3037 articles were collectively identified from the six individual searches that were performed, with an average of 502 articles per NCD. After the preliminary screening and duplicate filtration, 136 articles for perceptual-motor function, 68 articles for language, 379 articles for learning and memory, 86 articles for social cognition, 188 articles for complex attention and 64 articles for executive functions were considered for the subsequent screening based on the selection criteria. From this screening, 14 articles for perceptual-motor function, 10 articles for language, 87 articles for learning and memory, 17 articles for social cognition, 88 articles for complex attention and 29 articles for executive functions were considered. Additionally, there were 83 manually added references. All records for each NCD were combined, and duplicates were removed. Finally, a total of 256 studies were included in this review. This systematic review also contains more than 70 introductory and mechanistic references, which are not shown in the flow chart.

Plant-derived nootropics and perceptual-motor functions

Perceptual and motor functions include cognitive processing that is performed during visual perception, visuoconstructional reasoning and perceptual-motor coordination. However, in this paper, we also considered the effects of PDNs on physical activity, balance and coordination, which are considered extensions of the NCD of perceptual and motor function. Of note, impairments in this NCD arise as an initial and core symptom in several neurodegenerative diseases, including Alzheimer's disease (AD), parkinsonism, Parkinson's disease (PD), Huntington's disease (HD) and motor neuron diseases (MNDs) (Albers et al. 2015; Gallart-Palau et al. 2014; Goutman 2017; Kalia and Lang 2015; Liewluck and Saperstein 2015; Pfeiffer 2016; Snowden 2017). Therefore, the effects of PDN substances on the prevention and mitigation of perceptual and motor impairments in these neurodegenerative conditions were also reviewed. *Gingko biloba* L. (Gb) and flavonoids were identified as potential nootropics that target perceptual and motor functions. Other less relevant nootropics with modulatory effects in this NCD are briefly reviewed in the 'Other plant-derived nootropics with modulatory effects on perceptual-motor functions' section in the supplementary materials.

Gingko biloba

Gb, also known as the maidenhair tree, is a gymnosperm categorized in the vegetable kingdom as a unique member of the Ginkgophyta division. This tree, native to China, has been widely farmed in the country as a source of food and therapeutic components mainly extracted from its leaves (van Beek 2002; Wong et al. 2016). Gb extracts have shown a major impact on the NCD of perceptual and motor functions compared to other reviewed nootropics (Figure 2); thus, all studies that were reviewed for effects of Gb-derived nootropics on this NCD are detailed in Table 1. Standardized Gb extracts have been largely suggested to act as effective vasomodulators by increasing blood flow to the brain and enhancing vascular permeability (Chan, Xia, and Fu 2007; Diamond et al. 2000). The cognitive impact of these vascular-related effects is manifold; although some reports have found that Gb extracts may possess the ability to improve gait stability (Gschwind et al. 2017), this effect may mechanistically occur as a secondary impact of enhanced microcirculation in the prefrontal cortex (Yoshitake, Yoshitake, and Kehr 2010). Although elderly individuals with mild cognitive impairment (MCI), movement disorders and/or perceptual alterations are the groups in which the neurocognitive and neuromotor effects of Gb have been most extensively investigated, the impact of the standardized extract of Gb leaves (EGb-761) in the prevention of decreased motor skills through improved neurovascular circulation cannot be overlooked and remains inconclusive (Zhang et al. 2016). In addition, EGb-761 was also shown to improve tardive dyskinesia, as evidenced by reductions in Abnormal Involuntary Movement Scale scores obtained

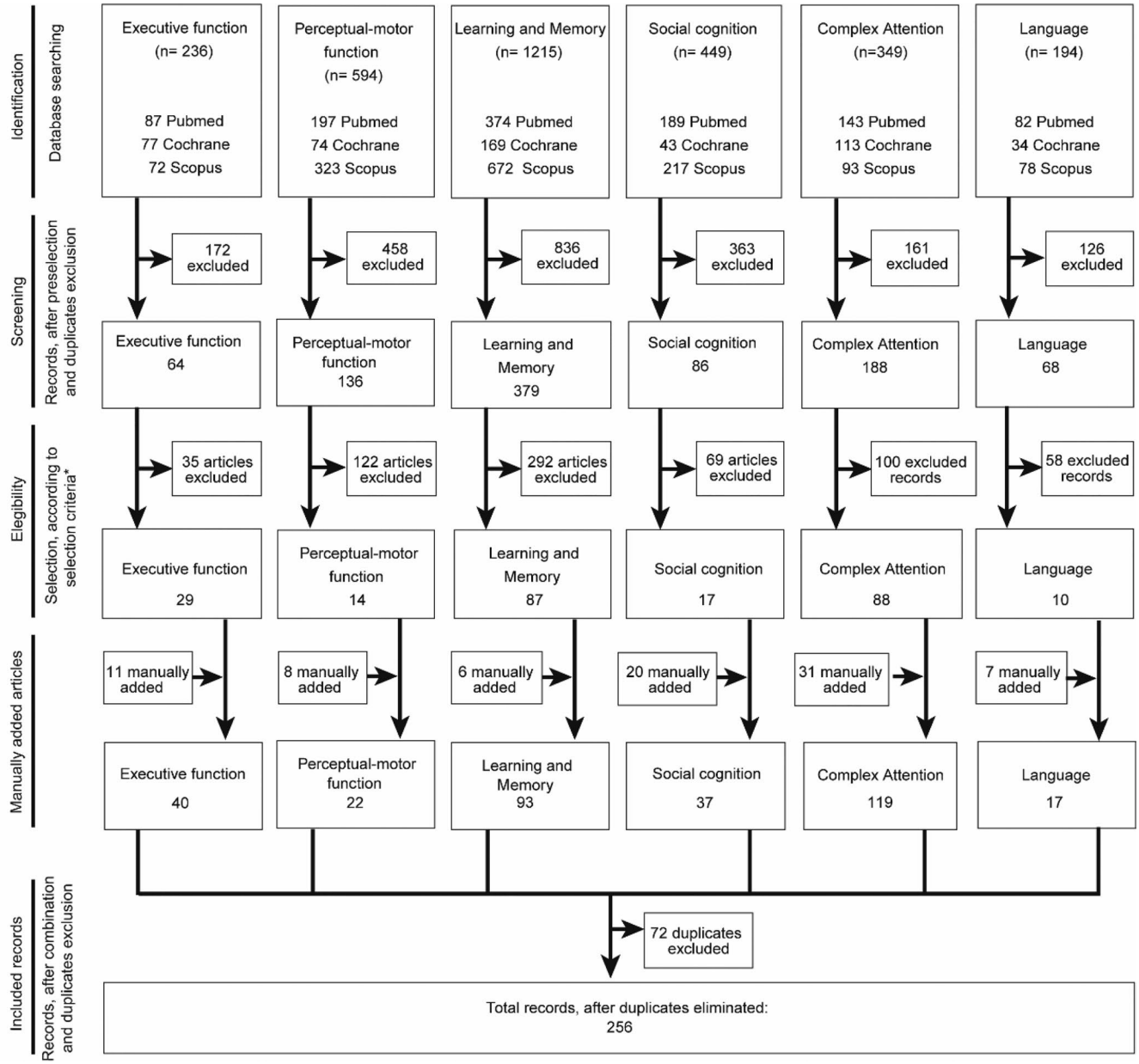

Figure 1. Flow chart of the systematic search strategy. The search strategy used in this systematic review was divided into five different steps: (1) Identification: An individual systematic search was performed for each NCD. (2) Screening: Articles were preselected based on the title, and the duplicates found in the different databases were excluded. (3) Eligibility: After preselection and duplicate exclusion, the remaining articles were screened and selected according to selection criteria*. (4) Manual addition: Articles coming from sources different from the systematic search were added manually for each NCD. (5) Included records: Articles for each NCD were combined, and duplicates were excluded. This systematic review also includes introductory references, which are not shown in this flow chart. *Selection criteria: publication date: Jan 2000–Nov 2021, participants: healthy and unhealthy humans of any age, measured effect directly related to at least one NCD, nonrecreational drugs, sample size n > 10, and articles available in English language.

in a randomized, double-blind, placebo-controlled trial with schizophrenia patients receiving antipsychotic treatment after 12 weeks of treatment with 240 mg/day of EGb-761 (Zhang et al. 2011).

In a related vein, Gb has been found to reduce annoying perceptual alterations such as tinnitus. The combination of tailored sounds and music with Gb was able to significantly reduce the emotional component associated with chronic tinnitus (Kim et al. 2017). Similarly, EGb-761 reduced the intensity and impact of tinnitus and dizziness in elderly individuals with MCI (Spiegel et al. 2018). Other authors have also found positive results regarding the effects of EGb-761 on tinnitus (Tziridis et al. 2014), and a conclusive systematic review indicated that standardized EGb-761, in particular, was a viable pharmacological treatment for tinnitus (Procházková et al. 2018). Notwithstanding, a systematic review assessing the effectiveness of Gb in patients affected by tinnitus concluded that Gb might be ineffective in patients with primary complaints of tinnitus and affirmed that the therapeutic effectiveness of Gb in reducing tinnitus hardly surpassed that of a placebo (Hilton, Zimmermann, and Hunt 2013).

Table 1. Summary of systematic reviews and clinical trials performed in humans studying the effect of *Ginkgo biloba* on perceptual-motor functions.

Study	Dose	Time	Participants	Effect	Reference
R DB PC Phase IV drug trial	240 mg extract, Symfona® forte, (120 mg twice/d)	6 months	50 patients (50–85 years), with mild cognitive impairment (MCI)	Improved dual-task-related cadence. Non-significant trends for dual-task-related gait velocity and stride time variability.	(Gschwind et al. 2017)
Overview of systematic reviews (n = 10)	Recommended dose: at least 240 mg/d EGb 761 extract	2 to 24 weeks	Prevention of cognitive decline, and MCI, AD and dementia patients.	240 mg EGb 761extract was effective reducing incidence in vertigo and tinnitus.	(H.-F. Zhang et al. 2016)
R DB PC	240 mg/d EGb-761 extract	12 weeks	157 schizophrenia with tardive dyskinesia	Decreased dyskinesia (AIMS total score). No differences in the PANSS total score or cognitive measures.	(W.F. Zhang et al. 2011)
Pilot study, not PC	160 mg Ginexin-F (80 mg twice/d) + notched music therapy	3 months	26 tinnitus, chronically distressed	Improved THI scores, particularly the emotional score in chronic tinnitus.	(Kim et al. 2017)
Review and Meta-analysis(n = 5) R PC clinical trials	240 mg/d EGb-761	20 weeks at least	Demented elders with tinnitus and dizziness	Effective in alleviating concomitant neurosensory symptoms (tinnitus and dizziness) in patients with dementia.	(Spiegel et al. 2018)
R DB	240 mg/d EGb or 1200 mg/d pentoxifylline	12 weeks	200 sub-chronic or chronictinnitus	EGb 761® and pentoxifylline were similarly effective in reducing the loudness and annoyance of tinnitus as well as overall sufferin, with lower rates of adverse events for EGb 761®.	(Procházková et al. 2018)

R: randomized; DB: double blind; PC: Placebo controlled; MCI: mild cognitive impairment; AD: Alzheimer's disease; AIMS: Abnormal Involuntary Movement Scale; PANSS: Positive and Negative Syndrome Scale; THI: Tinnitus Handicap Inventory (visual analogue scale that measures the effects of tinnitus in terms of loudness, noticeable time, annoyance, and disruption of daily life).

Flavonoids

Anthocyanins, flavanones, flavones and flavan-3-ols are flavonoid molecules that possess phenolic structures and are mainly be found in fruits and plant-derived products such as berries, citrus fruits, nuts, chocolate and red wine (Panche, Diwan, and Chandra 2016). Although the potentially beneficial effects of flavonoids in the NCD of perceptual and motor functions have been mainly observed in animal studies and thus remain out of the scope of this paper, a relevant epidemiological study that included a longitudinal follow-up of 20–22 years in a large cohort of 49,281 men and 80,336 women found a potential link between the consumption of dietary flavonoids and a lowered risk of PD, especially in males (Gao et al. 2012). Similarly, it was recently suggested that the effects of flavonoids on the neurovascular and motor systems may modulate the outcomes of aerobic exercise and recovery efficiency (Massaro et al. 2019). However, a systematic review of this hypothesis indicated that although flavonoids may act mildly by reducing the oxidative stress generated through aerobic exercise and altering the metabolic utilization of fats and carbohydrates in the body during exercise (Decroix et al. 2018), no clear conclusions can be obtained to support the assumption that the consumption of flavonoids improves exercise outcomes and recovery efficiency (Decroix et al. 2018). One study found that the acute ingestion of the flavonoid quercetin (a total dose of 1000 mg per day) improved neuromuscular function following resistance exercise, although no differences were observed in the presence and amount of blood markers of neuromuscular function (Patrizio et al. 2018). In another acute single-blind, randomized, crossover design study, 500 ml of flavonone-rich orange juice improved psychomotor processing in healthy young adults (Lamport et al., 2016), an effect justified by an observed increase in brain perfusion in the frontal gyrus. Psychomotor skills were also improved after the chronic consumption of 400 mg of grape seed polyphenol extract over 12 weeks, as reported in a randomized, placebo-controlled, parallel-groups acute-on-chronic trial (Bell et al. 2020). Similarly, Crataegus berry extract combined with D-camphor improved the results obtained in the digit symbol test, which measures visuomotor coordination and visual short-term memory (Schandry and Duschek 2008). Finally, a review concluded that the main effects of flavonoids on perceptual and motor functions were associated with acute ingestion of these compounds (Bell et al. 2015) at dosages ranging from 400 mg to 990 mg.

Plant-derived nootropics and language-related cognition

Language has been considered by *cognitive linguistics* as a phenomenon that is integrated across a diverse set of human cognitive abilities, such as perception, memory and categorization (Evans 2012). Based on this principle, nootropics targeting other cognitive functions, as cited above, may also act in the cognitive domain of language. To our knowledge, there are no clinical trials specifically assessing the activity of PDNs on language-related cognition. Nonetheless, we report here multiple clinical trials in which certain aspects of language-related cognition were assessed following the administration of the ayurvedic herb Bm. Other nootropics with cognitive enhancing activity, such as *Curcuma longa* L. (turmeric), Gb or the fungus lion's mane, are commonly used to treat cognitive deficits, including attention, memory, executive functions, perception and psychomotor functions, as well as language, in patients suffering from neurodegenerative and neurological diseases or unhealthy aging conditions (Froestl, Muhs, and Pfeifer 2012).

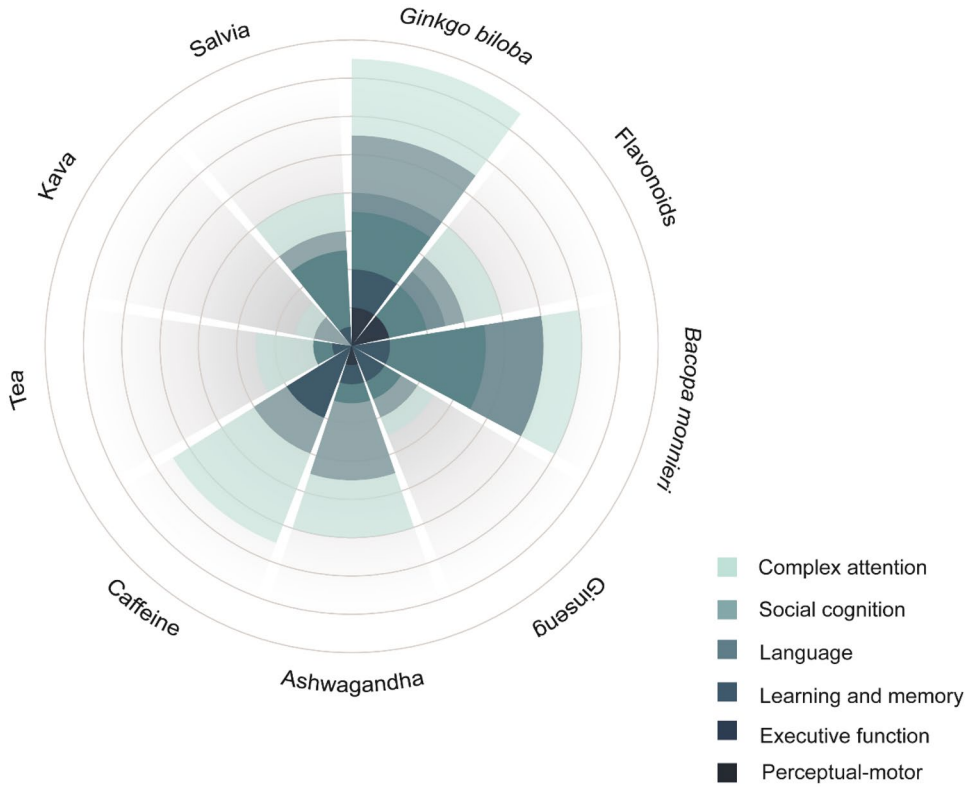

Figure 2. Radar chart displaying the evidence rating of the main nootropics for every NCD. Evidence rating of every nootropic for each NCD was calculated as a number from 0 to 5. To calculate the rating, the number of eligible studies showing positive results was counted: up to five studies were counted as 1 point, and 5 or more studies were counted as 5 points. Additionally, points were subtracted according to the following criteria: no studies available in healthy humans: −1 point; studies showing no effect or negative effects were considered as follows: 1–3 studies showing no effect: −1 point, 4–6 studies showing no effect: −2, >6 studies showing no effect: −3 points. Only clinical trials were considered for the evidence rating calculation. Reviews, systematic reviews, and studies in animals or examining the mechanism were not considered.

Although nootropics that are capable of improving brain plasticity may facilitate language learning and improvement, no clinical studies have been performed to prove this potential clinical association. Other nootropics with modulatory effects in this NCD are briefly reviewed in the 'Other plant-derived nootropics with modulatory effects on language-related cognition' section in the supplementary materials.

Bacopa monnieri

The perennial creeping herb plant Bm, commonly known as *Brahmi*, has been traditionally used in Ayurvedic medicine as a memory enhancer for thousands of years. In this paper, Bm was identified as the nootropic drug that has been used in the largest number of studies evaluating its effects in the language NCD and has been revealed as the nootropic drug with the greatest effectiveness on this NCD, as detailed in Table 2 and Figure 2. Notwithstanding, the existing clinical trials assessing the action of Bm in humans have mainly focused on the enhancement of cognition in children and young people, which has been extensively reviewed (Kean, Downey, and Stough 2016). A dose of 150 mg of a standardized extract of Bm (Bacognize) administered twice daily for six weeks was tested in a randomized, double-blind, placebo-controlled, noncrossover, parallel trial (Kumar et al. 2016). The obtained results indicated that Bm significantly improved language comprehension in the young adult population (Kumar et al. 2016). Similarly, Bm improved the capacity to identify and assimilate written letters by healthy subjects 1 to 2 hours after the consumption of the standardized Bm extract CDRI-08, with dosages ranging from 300 to 650 mg (Benson et al. 2014). Furthermore, it was found that a single daily dose of CDRI-08 significantly improved short-term verbal memory in young subjects with a lower range of intelligence quotients (Usha et al. 2008). Prolonged consumption of CDRI-08 also showed improvement in learning capacities involving language and written concepts in healthy subjects compared to placebo supplementation in a double-blind clinical trial (Stough et al. 2001b). The capability of Bm to improve language has also been tested in children and adolescents suffering from attention-deficit/hyperactivity disorder (ADHD). These studies found that CDRI-08 significantly improved language behavioral capacities, including word and sentence repetition, and logical memory in these subjects (Usha et al. 2008; Jauhari et al. 2001; Negi et al. 2000). Recently, Prabhakar et al. found that Bm consumption obtained similar results to donepezil treatment in MCI and AD subjects regarding the assessment of verbal fluency-controlled oral word tests, although this study included a small number of participants, and larger cohorts are required to verify this hypothesis (Prabhakar et al. 2020).

Table 2. Summary of clinical trials and systematic reviews included from the systematic search studying the effect of *Bacopa monnieri* L. Pennell on language.

Study	Dose	Time	Participants	Effect	Reference
Systematic review (n = 5 studies)	100–1050 mg/d	4–12 weeks	Children and adolescents (4–18 years) with ADHD	Significant and consistent improvements in language behavior, memory, hyperactivity and attention. Small to medium size effects.	(Kean, Downey, and Stough 2016)
R PC DB	300 mg/d (150 mg twice/d)	6 weeks	60 medical students (19–22 years)	Improvement language comprehension.	(Kumar et al. 2016)
DB PC independent-group design	300 mg/d CDRI 08 extract	5 and 12 weeks	46 healthy (18–60 years)	c information (IT task), learning rate and memory consolidation (AVLT), involved in language and written concepts, with maximal effects after 12 weeks.	(Stough et al. 2001b)

ADHD: Attention deficit hyperactivity disorder; R: randomized; DB: double blind; PC: Placebo controlled; IT task: measures speed of visual information processing; AVLT: Auditory Verbal Learning Test.

Plant-derived nootropics and learning and memory

Learning and memory are fundamental adaptive processes that define identity, independence, and quality of life. These cognitive processes have been core targets of nootropics since ancient times. The effects of certain nootropics on this NCD have been scientifically proven. The most common actors in this corpus of scientific research include Gb, phenolic compounds, Bm, ashwaghanda, plants from the genus *Salvia* L. (commonly known as sage) and *Hypericum perforatum* L., also known as St. John's wort, among other less studied nootropics, which are reviewed collectively in the section 'Other plant-derived nootropics with modulatory effects on memory' in the supplementary materials of this systematic review.

Ginkgo biloba

Aging, considered a biological process, exerts major negative impacts on the cognitive capacities of learning and memory (Gallart-Palau et al. 2019b; Mix and Crews 2002). Gb has been commonly revered as the memory plant in the East, and traditional medicines in Eastern societies have prescribed extracts of this tree to preserve memory and avoid the harmful effects of aging-associated cognitive decline. The consumption of Gb extracts in modern societies has extended worldwide (including Eastern and Western countries). Nonetheless, the conclusions obtained from the wide range of studies that have been performed to test the nootropic actions of Gb on learning and memory have shown major discrepancies. A double-blind, placebo-controlled, randomized trial performed to evaluate any potential effects of Gb in the NCD of memory in a cognitively healthy population of seniors over 60 years of age found that the extract of Gb leaves, EGb-761, was able to improve diverse aspects of memory, such as free recall, the recognition of noncontextual material and visual memory (Mix and Crews 2002). Other authors, in a comprehensive meta-analysis, found positive effects of Gb on memory in elderly individuals suffering from dementia (Yang et al., 2015). These results were obtained in elderly individuals, and we cannot assume that Gb is useful in preventing the progression of cognitive decline, as it was reported that subjects treated with a standardized commercial Gb extract (Thorne Research, Inc.) showed a higher risk of neurovascular alterations and ictus (Dodge et al. 2008). In contrast, several studies indicated the dose-dependent ability of Gb in improving memory skills in healthy young volunteers (Kennedy et al., 2007b; Kennedy, Scholey, and Wesnes 2001b; Naprienko 2014), while other found no significant effects (Canter and Ernst 2007; Nathan et al. 2002; van Dongen et al. 2000). Additionally, Gb seems to display synergistic effects, improving cognitive function when combined with dangshen (*Codonopsis pilosula* Nannf.) at a dose of 40 mg of Gb extract + 75 mg of dangshen glycosides (Singh et al. 2004). Although these studies have differing results, the combination of the available research suggests that Gb can be useful for enhancing learning and memory.

Phenolic compounds

Phenolic compounds form a wide family of small molecules that are ubiquitously present in plant tissues. Their common molecular feature is the presence of hydroxylated aromatic rings in their structures (Motilva, Serra, and Macià 2013; Rubió et al. 2014; Serra 2012; Swanson 2003). Phenolic compounds are classified into multiple subclasses according to the number of phenol rings and chemical groups bound to their structure. Flavonoids, a subclass of phenolic compounds with a 15-carbon skeleton formed by two phenyl rings and a heterocyclic ring, display multiple bioactivities, including antioxidant, anti-inflammatory and specific modulatory activities that act on several essential cell signaling pathways. For example, these compounds are able to modulate the phosphatidylinositol 3-kinase (PI3K/AKT) pathway, act on mitogen-activated protein kinase (MAPK), modulate pro-survival transcription factors and induce certain hippocampal gene expression, which affect the phosphorylation of tau proteins, among other key memory and AD-related activities (for further information on the mechanisms of flavonoids in the central nervous system (CNS), see the extensive reviews performed by Bakhtiari et al. (2017) and Spencer, Vauzour, and Rendeiro (2009)).

A wide array of phenolic compound-rich products, generally enriched in flavonoids, was found to improve multiple

memory- and learning-related aspects of cognition in healthy subjects and subjects suffering from dementia (Bakhtiari et al. 2017; Spencer 2010; Uddin et al. 2020; Whyte et al. 2021). Flavonoids are generally tested in the form of juices obtained from fruits, mainly berries. Cranberry juice, one of the plant-derived and phenolic compound-rich products that was analyzed, induced a nonstatistical but self-reported improvement in the abilities to remember and think, energy levels and mood in cognitively healthy seniors who consumed 32 ounces/day of cranberry juice in a double-blind, placebo-controlled, randomized trial (Crews et al. 2005). On the other hand, grape juice (acute intake of 230 mL of purple grape juice) consumption was tested in healthy young adults who showed significant improvements in memory, reaction times and ratings of calmness (Haskell-Ramsay et al. 2017). Likewise, the anthocyanin-rich extract obtained from haskap (*Lonicera caerulea* L.), a less-known berry native to Siberia and northeastern Asia, also improved episodic memory in elderly individuals, possibly due to the classic vasodilatory effects exerted by anthocyanins (with a high dose of 400 mg of anthocyanins) (Bell and Williams 2019). Incipient temporal hypoperfusion mechanisms and endothelial dysfunction, even at previously undetectable levels, have been recently associated with the appearance of AD and cognitive decline (Dutta et al. 2017; Gallart-Palau, Guo, et al. 2020; Gallart-Palau et al. 2019a; Gallart-Palau, Serra, and Sze 2020). Nonetheless, although the modulatory effects of flavonoids on episodic memory have not yet been well described, they seem to be more robust in children and in elderly individuals (Bell et al. 2015). Related to the vasodilatory effects of flavonoids, one study reported improved cerebral brain perfusion, predominantly in the anterior cingulate cortex and the central opercular cortex of the parietal lobe, after the consumption of an enriched flavonoid drink containing 494 mg of flavonoids. Of note, this effect, observed in volunteers and evaluated through functional magnetic resonance imaging, showed a positive correlation with the administered dose of flavonoids (Lamport et al. 2015). On the other hand, blueberry juice (500 mL per day), taken within 14 preoperative days before general anesthesia, also exerted neuroprotective action during the postoperative period, protecting against the characteristic anesthesia-induced short-term impairments in verbal memory and selective and divided attention (Traupe et al. 2018), a fact that is relevant especially for elderly individuals who suffer most of the detrimental cognitive effects of anesthesia.

A standardized extract containing green tea combined with L-theanine from the tea plant *Camellia sinensis* (L.) (LGNC-07) has also been shown to improve memory and selective attention. This enhancement was accompanied by an increase in brain theta waves in multiple brain areas (the temporal, frontal, parietal, and occipital areas), which has been related to improved cognitive alertness (Park et al. 2011). Magnetic resonance imaging has also shown changes in short-term plasticity in parietal-frontal brain synergies, accompanied by increased working memory processing in a population that had experimentally consumed a whey-based soft drink containing green tea extract (Schmidt et al. 2014). The results obtained in another study performed in healthy women showed a positive modulation of reading span performance, observed 24 hours after the administration of a single dose of 5.4 g of green tea extract (with at least 45% epigallocatechin gallate) in women from 50 to 63 years of age. In contrast, the previously described nootropic effect was not observed in a younger population, with ages ranging from 21 to 29 years (Liu et al. 2018). Resveratrol (75 mg taken twice daily for 12 months) tested in a randomized controlled trial with postmenopausal women also led to improvements in verbal memory, verbal recall and overall cognitive performance (Thaung Zaw et al. 2019; Wong, Evans, and Howe 2017). In addition to verbal-related cognition, another study showed that cerebrovascular responsiveness was also enhanced in postmenopausal women with regular resveratrol supplementation (Evans, Howe, and Wong 2017).

More recently, an extract enriched in phenolic compounds from *Persicaria minor* (P. Minor (Huds.) Opiz) has demonstrated the capacity to improve visual memory and mood in MCI patients through a multicenter, randomized, double-blinded, placebo-controlled study that included 36 patients (Lau et al. 2020).

Bacopa monnieri

Although Bm could be included in the previous section due to its rich content in a specific family of phenolic compounds known as bacosides (Abdul Manap et al. 2019), Bm was considered independently because of its described relevant therapeutic activity and potential applicability in the modulation of the learning and memory NCD in conditions of health and disease (Abdul Manap et al. 2019; Dubey and Chinnathambi 2019; Stough et al. 2013). Bm was the nootropic that had the most significant effects on learning and memory, as detailed in Table 3 and Figure 2. A systematic review published in 2012 examining six randomized, controlled, clinical trials found that Bm displayed clear nootropic activity on free recall memory (Pase et al. 2012); similarly, a recent review article highlighted the nootropic effects of Bm bacosides on memory and learning (Banerjee et al. 2021). A randomized, double-blind, placebo-controlled, noncrossover, parallel trial performed with a young population of 60 medicine students for six weeks found that the Bm extract CDRI-08 (150 mg twice daily) significantly enhanced immediate recall and working memory (Kumar et al. 2016). Longer treatment with CDRI-08 at the same daily total dose (300 mg) also improved the processing of visual information, learning rates and memory consolidation in healthy subjects (Stough et al. 2001b). Of note, these authors highlighted that the maximum observed effect regarding enhancements in learning rates and memory consolidation were more significant toward the end of the treatment (Stough et al. 2001b). Furthermore, it was also shown in another study that a similar dose of CDRI-08, as used by Kumar et al., over a span of four months enhanced working memory and short-term verbal memory in children in an individualized education program (Usha et al. 2008). A higher dose of 450 mg of CDRI-08 administered daily for 12 weeks also improved attention and verbal memory in a

Table 3. Summary of clinical trials and systematic reviews included from the systematic search studying the effect of *Bacopa monnieri* L. Pennell on learning and memory.

Study	Dose	Time	Participants	Effect	Reference
Systematic Review (n = 6) R PC trials	300–450 mg/d, 3 different extracts	12 weeks	Adult humans without dementia or significant cognitive impairment.	Improvement in memory free recall. Evidence for enhancement in other cognitive abilities currently lacking.	(Pase et al. 2012)
Open label clinical trial	225 mg/d BacoMind®	4 months	28 low IQ (70–90) children	Enhancement of working memory, short term verbal memory, logical memory, memory related to personal life, visual and auditory memory.	(Usha et al. 2008)
R PC DB	300 mg/d (150 mg twice/d)	6 weeks	60 medical students (19–22 years)	Improvement in learning, memory, executive function and attention tasks.	(Kumar et al. 2016)
DB PC independent-group design	300 mg/d CDRI 08 extract	5 and 12 weeks	46 healthy (18–60 years)	Improved speed of visual information (IT task), learning rate and memory consolidation (AVLT), and state anxiety, with maximal effects after 12 weeks.	(Stough et al. 2001b)
R DB PC	450 mg/d BacoMind®	12 weeks	65 elderly with memory complaints (50–75 years).	Enhancement in attention and verbal memory: digit span backward, list learning delayed recall, paired associates dissimilar delayed recall and visual retention-I tests.	(Barbhaiya et al. 2008)
R DB PC	300 mg/d whole plant dry extract	12 weeks	48 healthy elderly (65 or older, mean age 73.5 years)	Improved AVLT delayed word recall, Stroop test, CESD-10 depression and anxiety scores, and decreased heart rate. No effects on the DAT, WAIS digit task, mood, or blood pressure. No significant effect on memory after 12 weeks of administration.	(Calabrese et al. 2008)
DB PC crossover	320 mg/d and 650 mg/d CDRI 08 extract	Acute	24 healthy (18 to 56 years)	320 mg (not 650 mg) CDRI 08 improved performance in the Cognitive Demand Battery.	(Downey et al. 2013)
Review (11 R DB PC)	At least 200 mg/day	12 weeks to 12 months	Healthy subjects and AD patients	Moderate improvement of logical memory.	(Brimson et al. 2021)
R DB, parallel Phase-2 study	300 mg/day vs. donepezil 10 mg	12 months	48 patients (>50 years), diagnosed with MCI-AD or AD	No significant differences after 12 months of treatment	(Prabhakar et al. 2020)
Review	bacosides and bacopa saponins	–	–	Toxicity of Bm needs to be adecuately investigated in populations such as children, pregnant, lactating, elderly. Proper chemical characterization needs to be expanded besides bacoside A.	(Banerjee et al. 2021)

R: randomized; DB: double blind; PC: Placebo controlled; IT task: measures speed of visual information processing, AVLT: Auditory Verbal Learning Test, CESD-10: Center for Epidemiologic Studies Depression scale, DAT: Divided Attention Task, WAIS: Wechsler Adult Intelligence Scale.

population of elderly individuals with normal cognition. It was also reported that this treatment resulted in interaction effects between the groups and time on multiple tests, including the digit span backward test, list learning delayed recall test, paired associates dissimilar delayed recall test and visual retention-I test (Barbhaiya et al. 2008). In addition, a review showed that long-term treatment with a Bm extract also improved certain behavioral deficits associated with epilepsy, as it enhanced the performance on sentence repetition, logical memory and paired associate learning tasks by these subjects (Mathew et al. 2010).

It is also important to mention that other studies assessing the nootropic activity of Bm did not find any significant improvement in memory; for example, there was no reported improvement in a randomized, double-blind, placebo-controlled clinical trial performed with 54 healthy elderly subjects following a 12-week treatment with 300 mg per day of a Bm extract obtained from the dried aerial part of the plant with a minimum of 50% bacosides A and B (Calabrese et al. 2008). Brimson et al. found very recently in a systematic review that subjects taking Bm extracts were able to reach apparent improvement, but this did not reach a significant threshold in some studies including healthy subjects (Brimson et al. 2021). Similarly, when CDRI-08 dosing was assessed with regard to its effectiveness in the memory and learning NCD, it was found that although positive effects of Bm could be identified at doses up to 300 mg per day, higher doses did not yield any further positive effects (Downey et al. 2013). Finally, Prabhakar et al. recently found that the effects of Bm on the NCD of learning and memory could be comparable to those offered by a classic pharmacological treatment (Prabhakar et al. 2020).

Ashwaghanda

Ashwagandha is a *Solanaceae* Juss. plant that is highly appreciated in Indian Ayurvedic medicine as a tonic (considered

one of the most important Rasayana tonics in the Ayurveda millennial medicine corpus) (Singh et al. 2011). Extracts from this herb have commonly been obtained from the leaves, stem and roots of the plant, while common nootropic uses for these extracts involve improvements in sleep induction, mood and anxiety (Singh et al. 2009). A randomized, double-blind, placebo-controlled study in a population of elderly subjects with MCI demonstrated that supplementation with ashwaghanda root extract (300 mg twice daily for eight weeks) improved diverse aspects of the memory and learning NCD, including visual memory and verbal recall (Choudhary, Bhattacharyya, and Bose 2017).

Sage

Commonly known as sage, the genus *Salvia* L., with nearly 1000 species, is the largest genus from the mint plant *Lamiaceae* family. Extracts from many plants of this genus have been traditionally appreciated for their brain-enhancing potential in traditional medicine corpuses. Recently, based on scientific research, these extracts have become appreciated due to their cholinergic properties (Lopresti 2017; Tildesley et al. 2005b). The terpenoids contained in sage extracts possess cholinesterase-inhibiting abilities that has been related to improvements in cognitive performance in conditions of health and disease, including dementia-related conditions, such as AD (Miroddi et al. 2014). In healthy adults, an enhancement of secondary memory and attention task performance was reported after an intervention with sage, administered twice with a span of 7 days between dosages (Kennedy et al. 2011). In a placebo-controlled, double-blind, balanced, crossover study, the same dose of sage (50 µL of the essential oil) enhanced immediate word recall in healthy young subjects (Tildesley et al. 2003), and improved the speed of memory as assessed in a placebo-controlled, double-blind, balanced, crossover study experiment in the same experimental setting (Tildesley et al. 2005b). In addition, a significant improvement in secondary memory was reported after the administration of 333 mg of sage extract in healthy older adults (>65 years of age) (Scholey et al. 2008). Similar findings were also observed, although to a lesser extent, with lower and higher doses of the extract (ranging from 167 to 1332 mg) (Scholey et al. 2008). In subjects with mild to moderate AD, long-term treatment with sage essential oil over 4 months significantly improved scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) and Clinical Dementia Rating (CDR) scale. In this study, the authors also highlighted that sage essential oil seemed to reduce agitation in AD subjects, a potential and relevant effect that requires further investigation (Akhondzadeh et al. 2003).

St. John's wort

Hypericum perforatum L., commonly dubbed St. John's wort, is a rigid-stemmed glandulous herb with opposite leaves and yellow flowers. This plant has been extensively used in the therapeutic arsenal of different traditional medicines, including TCM. Therapeutic applications of St. John's wort have included tissue astringency, antisepsis, and healing, as well as sleep disturbances, depression and anxiety (Saddiqe, Naeem, and Maimoona 2010; Zirak et al. 2019). St. John's wort is generally used as an antidepressant, and multiple authors have investigated its effects on memory in healthy humans. In general, St. John's wort does not exhibit remarkable nootropic effects on memory. The results obtained in a double-blind, crossover, repeated-measures study performed with 20 healthy subjects showed a moderate impairing effect on the accuracy of numeric working memory and delayed picture recognition at the higher tested dose of 1800 mg (Ellis et al. 2001). Another randomized, double-blind, crossover study performed with 12 healthy subjects, with a dose of 255–285 mg of St John's wort extract (approx. 900 µg of hypericin content) taken three times daily for 14 days, did not show any conclusive effects on short-term memory (Siepmann et al. 2002). On the other hand, a single dose of 250 mg of hypericum (containing 0.5 mg of hypericin), tested in a randomized, double-blind, placebo-controlled trial with 82 healthy volunteer students, showed a positive effect on short-term verbal memory (Yechiam et al. 2019). Another study carried out in healthy subjects failed to find evidence for the modulatory effects of St. John's wort on working memory, although a significant increase in memory for positive words was reported (Warren, Cowen, and Harmer 2019). The nootropic effect of St. John's wort on memory was also tested in a study that involved volunteers engaged in smoking cessation, and no significant memory-related effects were observed (Camfield et al. 2013).

Plant-derived nootropics and social cognition

Social cognition is any cognitive process that is involved in social interactions with others (Frith and Blakemore 2006). In terms of pathology, this NCD is closely linked to psychosocial dysfunction in neurodevelopmental, psychological and psychiatric disorders such as autism, personality disorders (borderline personality disorder, avoidant personality disorder) and major depression (Knight and Baune 2019). Although it was initially thought that psychosocial dysfunction could be exclusively attributed to abnormal temperamental traits, it has been demonstrated that people with impairments in the social cognition domain often present deficits in social processing (Hill et al. 2008). In a milder form, and far from its implications in neuropsychiatric and major mental disorders, alterations in the social cognition domain can transform unavoidable social interactions and those requiring adaptations into a source of individual distress. Physiologically, the amygdala seems to be the brain region with major neurofunctional implications in social processing, especially in the processing of visual social stimuli (Adolphs, Sears, and Piven 2001).

Among the broad spectra of PDNs with the ability to act on this NCD (Sarris 2018), there are three PDNs with remarkable modulatory capacities. These nootropics, which are exhaustively reviewed in this paper, include Ashwagandha, *Curcuma longa* L. (turmeric), Gb. Other nootropics with

4

Table 4. Summary: included systematic reviews and clinical trials performed in humans, studying the effect of Ashwagandha (*Withania somnifera* (L.) Dunal) on social cognition.

Study	Dose	Time	Participants	Effect	Reference
Systematic review: R PC (n = 5 studies)	125 to 12,000 mg/d extract	2 weeks to 2 months	Anxiety	All studies observed greater score improvements (significantly in most cases) than placebo in anxiety or stress scales. None reported significant adverse effects.	(Pratte et al. 2014)
R DB PC	1,000 mg/d extract, as adjunctive treatment	12 weeks	66 schizophrenic patients, with depression and anxiety symptoms.	Reduction in symptoms of depression and anxiety, with medium size effects. Adverse events were mild and transient.	(Gannon et al. 2019)
R DB PC	500 mg/d as adjunctive treatment	8 weeks	60 (53 completed the study) bipolar disorder patients	Significant benefits for: digit span backward (auditory-verbal working memory, Executive function), Flanker neutral response time, and the social cognition response rating of the Penn Emotional Acuity Test. Mood and anxiety scale scores remained stable.	(Chengappa et al. 2013)
R DB PC	240 mg/d extract (Shoden)	60 days	60 stressed, healthy adults	Anxiolytic capacity: reduction in Hamilton Anxiety Rating Scale and Stress Scale −21. Decreased cortisol and DHEA-S, and increased testosterone in males.	(Lopresti et al. 2019)
Single center, prospective, R DB PC	300 mg/d of root extract	60 days	64 subjects with a history of chronic stress	Reduction in stress-assessment scales. Substantially reduced serum cortisol levels.	(Chandrasekhar, Kapoor, and Anishetty 2012)
Prospective, R DB PC	250 or 600 mg/d (125 or 300 mg twice/d)	8 weeks	60 (58) stressed, healthy adults	Reduction in perceived stress scale scores, improvement in sleep quality and reduced serum cortisol levels, with both doses.	(Salve et al. 2019)
R DB PC	600 mg/d (300 mg twice/d) root extract	4 and 8 weeks	52 subjects, with chronic stress and related disorders.	Reduction in stress and food cravings. Increased score in the Oxford Happiness Questionnaire. Reduced serum cortisol, body weight, and body mass index.	(Choudhary, Bhattacharyya, and Joshi 2017)

R: randomized; DB: double blind; PC: Placebo controlled; DHEA-S: dehydroepiandrosterone-sulphate; MCI: mild cognitive impairment.

modulatory effects on this NCD are briefly reviewed in the 'Other plant-derived nootropics with modulatory effects on social cognition' section in the supplementary materials.

Ashwagandha

Multiple human trials have shown the capability of ashwagandha to treat anxiety (Pratte et al. 2014), and extracts of this herb were the most influential in this systematic review for improving aspects of social cognition, as shown in Table 4 and Figure 2. Ashwagandha has also been tested as an adjuvant pharmacological treatment for psychiatric disorders. For example, its use in schizophrenia patients led to a significant reduction in symptoms of depression and anxiety assessed in a 12-week, randomized, placebo-controlled, double-blind study administering 1000 mg of an ashwagandha standardized extract (Gannon et al. 2019). Similarly, this herb improved auditory-verbal working memory (as a measure of social cognition) in an 8-week, placebo-controlled, double-blind, randomized study with bipolar disorder patients with a dose of 500 mg/day of ashwagandha extract, taken together with psychopharmacological medication (Chengappa et al. 2013). Ashwagandha also displayed anxiolytic activity in bipolar disorder patients (Lopresti et al. 2019) and contributed to improved verbal hearing, reporting and reaction times in public settings (Chengappa et al. 2013). In stressed subjects, the antistress adaptogenic activity of ashwagandha has also been described as reducing stress-induced physical effects (Chandrasekhar, Kapoor, and Anishetty 2012; Salve et al. 2019). These studies were based on the analysis of the physiological effects of ashwagandha by measuring circulating serum cortisol levels, which were significantly reduced in the subjects receiving treatment with ashwagandha extracts. As a collateral effect, ashwagandha also seems to hold promise for helping in the management of body weight in adults under chronic stress (Choudhary, Bhattacharyya, and Joshi 2017).

Turmeric

Similar to ashwagandha, the rhizome of the flowering plant turmeric from the ginger *Zingiberaceae* family originated in Southwest India (Omosa, Midiwo, and Kuete 2017), and curcumin, its primary bioactive diarylheptanoid antioxidant bioactive compound, is widely classified as nootropic due to its notable antidepressant and anxiolytic abilities (Al-Karawi, Al Mamoori, and Tayyar 2016; Asadi et al. 2020; Esmaily et al. 2015; Fusar-Poli et al. 2020; Kanchanatawan et al. 2018; Sanmukhani et al. 2014). The effectiveness of curcumin has been successfully and consistently proven in patients with major depression (Al-Karawi, Al Mamoori, and Tayyar 2016; Lopresti et al. 2014; Sanmukhani et al.

2014; Yu et al. 2015), as well as in subjects suffering from other chronic and proinflammatory diseases, such as subjects with diabetes mellitus with peripheral neuropathy (Asadi et al. 2020) and obesity complications (Esmaily et al. 2015). In general, curcumin efficiently mitigated anxiety and depressive symptoms in these subjects with a prolonged treatment of at least 6 weeks and with a high dosage of 1 g/day. The detailed anxiolytic and mood stabilizing abilities of curcumin have been extensively studied, and a study found that superior efficacy could be attributed to curcumin treatment in a subgroup of psychiatric patients with atypical depression (Lopresti et al. 2014). This fact indicated that the psychophysiological substrates of curcumin in the CNS may be very specific and that the nootropic abilities of the extract, especially related to euthymia, may spread from a central core of substrates, a fact that requires further research. It has also been suggested that curcumin possesses adjuvant activity with medicinal drugs in the treatment of anxiety (Fusar-Poli et al. 2019; Lopresti et al. 2014), although larger clinical trials should be performed to prove this ability. Several studies have demonstrated the anti-inflammatory activity of curcumin in different chronic human diseases, including rheumatoid arthritis (Daily, Yang, and Park 2016) and inflammatory bowel disease (Vecchi Brumatti et al. 2014). Similarly, the adjuvant activity of other natural substances, such as saffron (Lopresti and Drummond 2017) or piperine (Panahi et al. 2015), in conjunction with curcumin has also been tested. Nonetheless, no conclusive results were obtained from these studies regarding the adjuvant activity of these substances in combination with curcumin extracts regarding the NCD of social cognition.

Gingko biloba

Gb leaf extracts have been used for centuries for their multiple pharmacological qualities, and their antidepressant effects are one of the most appreciated aspects. Different clinical trials have been performed over the last thirty years to assess the activity of Gb as an adjuvant to treat depression and anxiety symptoms for different human diseases, including depression in the elderly population (Dai et al. 2018), generalized anxiety disorder and adjustment disorder (Woelk et al. 2007), MCI with neuropsychiatric symptoms (Gavrilova et al. 2014), dyscirculatory encephalopathy and cognitive impairment (Litvinenko, Naumov, and Odinak 2014), MS (Johnson et al. 2006) and AD (Le Bars et al. 2002). It has been clinically demonstrated that Gb extracts improve depression and anxiety symptoms, and its effects seemed to impact the expression of the brain injury marker serum S100B, suggesting a restoration of neurological function with a dose of 19.2 mg of Gb extract taken three times daily (Dai et al. 2018). A standardized extract of Gb (LI-1370) has also been tested in healthy postmenopausal women at a dose of 120 mg/day for 6 weeks, leading to improved ratings of mood and sleepiness (Elsabagh, Hartley, and File 2005). Moreover, a positive correlation was detected when treating anxiety disorder with varying doses of the standardized Gb extract EGb-761 (Woelk et al. 2007). In addition, there was a clear influence on the severity of cognitive impairment in AD patients on the effectiveness of Gb (Le Bars et al. 2002). A more marked enhancement of social functioning was observed in patients with very mild to mild cognitive decline, while in patients with more severe baseline symptomatology, the effect of Gb could be considered to stabilize disease progression (Bars 2003; Le Bars et al. 2002).

Plant-derived nootropics and complex attention

Attention covers the capacity to selectively focus on one specific stimulus while ignoring others (McDowd 2007; Shipp 2004). There are different types of attention depending on the nature of the task performed, including sustained attention, selective attention, divided attention and attention switching (McDowd 2007). As detailed in the following sections, the most studied nootropic substances regarding the NCD of attention are caffeine, Gb, ashwagandha, Bm, French maritime pine bark (*Pinus pinaster* Aiton) and salvia. Other nootropics with researched modulatory effects on this NCD are briefly reviewed in the 'Other plant-derived nootropics with modulatory effects on complex attention' section in the supplementary materials.

Caffeine

Caffeine is a methylxanthine that is present in more than sixty plants, with coffee being a brewed drink prepared from the roasted beans of the *Coffea arabica* L. plant and the most popular caffeine-containing drink worldwide (Lee and Balick 2006). In addition to coffee, caffeine is also present in other plant-derived foods and drinks, such as tea, chocolate and guarana (Verster and Koenig 2018). Caffeine was the most relevant nootropic substance affecting the NCD of attention, as revealed in Table 5 and Figure 2. Dietary caffeine is rapidly absorbed through the gastrointestinal tract and transported to the bloodstream, showing a peak plasma concentration at T_{max} of 30–120 min after consumption (Carrillo and Benitez 2000). Caffeine is the most human-consumed psychostimulant substance in the world (Daly, Holmén, and Fredholm 1998). Oral caffeine produces rapid positive inotropic and chronotropic effects on the cardiovascular system, leading to an increased heart rate and conductivity, together with augmented locomotor activity stimulation and anxiogenic-like effects (Cappelletti et al. 2015). In the CNS, caffeine is an activator of dopaminergic and glutamatergic functions. This effect takes place due to the antagonistic effects of caffeine at the inhibitory receptors of adenosine A1 and A2 (Ferré 2008). Brain imaging has also shown activation in multiple brain areas, including the left cerebellum, putamen, thalamus, insula and right primary motor cortex, after oral caffeine intake (Park et al. 2014).

The action of orally administered caffeine regarding the NCD of attention has been extensively examined in humans, as detailed in this section. Caffeine has been experimentally administered to humans in a wide variety of formulations, including pills (Wilhelmus et al. 2017), infusions or brewed

Table 5. Summary of systematic reviews and clinical trials performed in humans, studying the effect of caffeine on complex attention.

Study	Dose	Time	Participants	Effect	Reference
Not PC	200 mg caffeine pill	Acute	14 healthy subjects (mean age 30 ± 7 years)	fMRI and PET scan showed modulation (blood oxygenation level and metabolic activity) in brain regions implicated in cognitive functions like attention.	(C.A. Park et al. 2014)
R PC	Small dose: 60 mg	Acute, up to 45 minutes post ingestion	82 healthy adults, low or non-caffeine-consuming (40–60 years)	Improvement in sustained attention, peak saccadic velocity and reaction time performance. Decreased error rate. Increased feelings of alertness, contentment, and overall mood.	(Wilhelmus et al. 2017)
DB PC	2 mg/kg + regular caffeine daily dose	Acute, 30 minutes post ingestion	68 non-withdrawn, regular caffeine consumers (20–62 years)	Improved mood and cognitive performance. Increased scores in categorical search and repeated digit tasks, and not significant in focused attention or simple reaction time tasks.	(Christopher, Sutherland, and Smith 2005)
DB PC	600 mg	Acute, during 3 days	50 healthy young adults, awake for 54.5 h (from 6:30 a.m. day 1 to 1:00 p.m. on day 3)	Performance and alertness were improved by modafinil (220 and 400 mg) and caffeine, in conditions of sleep loss. Modafinil did not appear to offer advantages over caffeine.	(Wesensten et al. 2002)

R: randomized; DB: double blind; PC: Placebo controlled; fMRI: functional Magnetic Resonance Imaging; PET: Positron Emission Tomography.

drinks (Christopher, Sutherland, and Smith 2005; Dietz, Dekker, and Piqueras-Fiszman 2017), foods (i.e., matcha tea as an ingredient in food preparations (Dietz, Dekker, and Piqueras-Fiszman 2017)), guarana (Kennedy et al. 2004; White et al. 2017)), or in conjunction with sugars (Rao, Hu, and Nobre 2005; Scholey et al. 2014; Scholey and Kennedy 2004; Ullrich et al. 2015) or taurine (Alford, Cox, and Wescott 2001; Scholey and Kennedy 2004; Seidl et al. 2000; Wesnes et al. 2017), generally in energizing drinks, as well as with L-threonine (Haskell et al. 2008; Haskell et al. 2007; Kelly et al. 2008), theacrine from *Camellia kucha* (Hung T. Chang) (Kuhman, Joyner, and Bloomer 2015) or *Panax ginseng* C.A. Mey (Kennedy et al. 2004) among others. A systematic review and meta-analysis that included 11 randomized placebo-controlled human studies concluded that there was a synergistic effect on attentional switching accuracy when caffeine and L-theanine were combined within a 2-hour timespan (Camfield et al. 2014). Caffeine has also been tested in humans by using mouth-rinse solutions, only exerting a likely beneficial effect on reaction time in healthy male subjects (De Pauw et al. 2015), and herbal-caffeinated chewing gum (20 mg caffeine/serving), but caffeine administered by this strategy improved memory but not concentration (Davidson 2011).

The main effects of caffeine in the NCD of attention include improved sustained visual selective attention and target-specific attention, with increased behavioral performance in terms of accuracy and reaction speed (Kahathuduwa et al. 2018; Rao, Hu, and Nobre 2005). In combination with alcohol, the boosting effects of caffeine on attention were significantly reduced, introducing a characteristic shift in the speed/accuracy tradeoff (Benson, Tiplady, and Scholey 2019). In contrast, when combined with *Alpinia galangal* (L.) Willd., the effects of caffeine on attention were sustained for more than 3 hours, and the typical caffeine crash was also prevented (Srivastava, Mennemeier, and Pimple 2017).

The consumption of moderately high doses of caffeine (~600 mg) has been shown to have relevant positive effects on vigilance and alertness and was as effective as some commonly prescribed medications (i.e., modafinil and amphetamines) that are used to improve attention (Wesensten et al. 2002). Similar doses of caffeine have also been evaluated and shown to improve performance and alertness in soldiers affected by sleep deprivation (Kamimori et al. 2015; Tikuisis et al. 2004). For soldiers maintaining sustained surveillance for 3 nights with periods of four hours of sleep, the continued administration of caffeine (800 mg/day, administered in repeated smaller doses of 200 mg) significantly improved their cognitive and attention functions (Kamimori et al. 2015). Caffeine also improved the target detection ability of the subjects. Nonetheless, no improvements were reported in the psychomotor aspects of marksmanship in subjects performing shooting tests under sleep deprivation (Tikuisis et al. 2004). In contrast, caffeine from guarana exhibited a better response to acute mood and cognition at much lower doses (<75 mg of guarana extract), pointing toward a synergistic action between caffeine and other guarana bioactive compounds that act on the NCD of attention (Haskell et al. 2007).

Gingko biloba

Regarding the use of Gb to improve attention-related cognition, in a recently published updated review assessing human trials performed since the 1980s with healthy people as well as AD patients, it was concluded that Gb was able to improve certain clinical symptoms that are associated with cognitive decline, including attention, memory loss, alertness, vigilance and mental fluidity (Liu et al. 2020). These positive effects may be related to the ability of Gb to inhibit monoamine oxidase (MAO) enzymes in the CNS (Santos et al. 2003).

Using a randomized, double-blind methodology with healthy subjects (with ages ranging from 18 to 40 years old), participants taking a tablet of 2000 mg of Gb EGb-761 extract (containing 120 mg of the active ingredient) for 30 days reported improvements in memory and attention, together with enhancements in cognitive clarity, but only as positive subjective effects (Stough et al. 2001a). In elderly healthy subjects, long-term treatment for 8 months with a nonstandardized Gb extract (the composition of the extract

can be obtained from (Santos et al. 2003)) improved several aspects of cognitive performance, including attention processes related to task execution speed (Santos et al. 2003). According to the results obtained from one placebo-controlled, double-blind study, an accurate dosage is key to obtaining the desired results with Gb, such that better boosting capacities on attention and pattern-recognition memory tasks were obtained after a single dose of 120 mg of standardized Gb extract (LI-1370) but not after prolonged treatments with Gb (Elsabagh et al. 2005). In a related vein, a detrimental effect on reaction speed in attention tasks with the common dosage of 120 mg of standardized Gb extract (GK-501) administered daily was observed in another study (Kennedy et al., 2007c). Nonetheless, the same authors in previous works found dose-dependent improvements in attention speed when testing higher doses of this nootropic (over 240 and up to 360 mg of GK-501) (Kennedy, Scholey, and Wesnes 2000). Thus, further studies are required to assess the optimal dosage that can maximize the nootropic effects of Gb on the NCD of attention.

The effects of Gb have also been tested in postmenopausal healthy women. In this specific population, one week of treatment with 120 mg of standardized Gb extract (LI-1370) significantly improved sustained attention measured by using the Paced Auditory Serial Addition Test (PASAT). However, these positive results were not obtained at the fastest presentation speed (Hartley et al. 2003). In a similar study, Gb (LI-1370) only led to cognitive boosting effects in stage 2 postmenopausal women with poorer cognitive performance (Elsabagh, Hartley, and File 2005).

The use of Gb to ameliorate cognitive impairment in those with neurodegenerative and neurological diseases has also been examined over the last twenty years, and this research topic was the focus of multiple review articles (Kaschel 2009; Singh et al. 2017; Wang et al. 2010). In subjects with non-AD-type age-related MCI, one study reported that Gb was safe and effective for improving memory and concentration (Bäurle, Suter, and Wormstall 2009). A 90-day intervention using Gb in the form of a standardized Gb extract (EGb-761) with 40 mg taken three times daily positively modulated mood, memory, information learning and working capacity in young adults with cognitive impairment symptoms, including headache and memory and attention impairments (Naprienko 2014). Similar results were obtained when administering a nonstandardized Gb extract to brain tumor patients (120 mg, three times per day), although these patients were reported to have a higher rate of dropout under this treatment (Attia et al. 2012).

Although positive results have been reported regarding the ability of Gb to improve memory-related cognition in healthy subjects as well as in those with some human diseases (Burns, Bryan, and Nettelbeck 2006), multiple human studies did not obtain conclusive results on attention when testing the cognitive enhancing effects of Gb in healthy subjects or patients suffering from multiple sclerosis (Canter and Ernst 2007; Hartley, Elsabagh, and File 2004; LaSala et al. 2015; Lovera et al. 2007; Snitz et al. 2009; Solomon et al. 2002).

The synergies between Gb and other nootropics have also been extensively investigated over the last twenty years. Gb was tested in conjunction with Bm (120 mg of a Gb extract + 300 mg of a Bm extract) in 85 healthy subjects in a randomized, double-blind, placebo-controlled, independent group study for four weeks, without conclusive results on attention-related cognition (Nathan et al. 2004). Gb was similarly tested in conjunction with ginseng (60 mg of a standardized Gb extract (GK-501) + 100 mg of a standardized ginseng extract (G-115)) in healthy middle-aged volunteers with no positive results on attention, which was measured with a conjunction of tests from the Cognitive Drug Research computerized cognitive assessment system (Wesnes et al. 2000). In a series of studies performed by Kennedy and colleagues, it was found that Gb (GK-501) alone was able to significantly improve the speed of attention in a dose-dependent manner. Nonetheless, when Gb was administered in conjunction with ginseng, this effect was reversed but accompanied by a significant improvement in the quality of memory (Kennedy, Scholey, and Wesnes 2001a). The decrease in speed of attention observed when administering Gb and *P. ginseng* seemed to be produced by ginseng itself, as this effect was also reported for ginseng alone (Kennedy, Scholey, and Wesnes 2001b). In a more recent study, the same authors reported a negative effect of Gb on attention speed (Kennedy et al. 2007b), although this negative modulation was significantly improved when Gb was combined with phosphatidylserine (Kennedy et al. 2007a). Taken together, the reviewed studies demonstrate that the synergistic effects of Gb with other nootropics on attention speed and other attention-related cognitions should be further investigated and validated in humans to clarify the currently inconclusive results (Reay, Schaik, and Wilson 2019).

Ashwagandha

The effects of ashwagandha on the NCD of attention have also been assessed through multiple human studies and trials, mainly focused on patients with attention deficits caused by cognitive decline (Ng et al. 2020). The administration of 300 mg of ashwagandha root extract for four weeks improved sustained attention and information processing speed in subjects diagnosed with MCI. Prolonged treatment (up to eight weeks) with the same dosage further improved sustained attention in these elderly subjects (Choudhary, Bhattacharyya, and Bose 2017). Similarly, in healthy adults, ashwagandha taken twice daily for 14 days improved simple reaction test and choice discrimination test scores, which assess attention and sensory-motor performance (Pingali, Pilli, and Fatima 2014). A significant gain in attention and working memory was also reported in diagnosed euthymic bipolar subjects when they were treated with an increasing dose of ashwagandha, increasing from 250 mg to 500 mg, administered for eight weeks (Chengappa et al. 2013). In a related manner, the synergy between ashwagandha (150 mg of the dry herb extract Adaptra ® Forte) and *Andrographis paniculate* (Burm. f.) Wall. ex Nees (400 mg of a dry herb

extract) taken for 2 and 4 weeks was investigated for effects on the electrical activity of the brain in a randomized, double-blind, placebo-controlled, two-armed crossover study with 16 elderly subjects suffering from MCI (Dimpfel et al. 2020). The results of this study demonstrated that both herb extracts taken together exerted a significant anxiolytic effect without sedation and a significant improvement in cognitive performance. Nonetheless, no statistical significance was obtained with the acute intake of the adaptogenic combined extract (Dimpfel et al. 2020).

Bacopa monnieri

The ayurvedic memory enhancer Bm has also been shown to led to significant improvements in attention-related cognition (Stough et al. 2013), particularly in attention speed (Kongkeaw et al. 2014). In healthy subjects, chronic treatment for 12 weeks with 300 mg of a Bm extract (CDRI-08) improved cognitive processes that depend on information input from the environment, including learning and memory, and visual information processing capacity (Stough et al. 2001b). In addition, acute treatment with a Bm extract (CDRI-08, 640 mg daily) in healthy subjects significantly improved performance in divided attention tasks (Downey et al. 2013). Bm has commonly been administered in ayurvedic medicine together with an extract from the perennial *Apiaceae* plant, known as *Centella Asiatica* (L.) Urb., for the treatment of attention disorders, especially in children (Shinomol, Muralidhara, and Bharath 2011). Nonetheless, the effects of Bm in the NCD of attention may need further investigation, as several human studies, meta-analyses and systematic reviews have also reported variable or inconclusive results (Kean, Downey, and Stough 2016; Kongkeaw et al. 2014; Roodenrys et al. 2002; Sathyanarayanan et al. 2013). Some authors pointed out that the studies performed with Bm on attention-related cognition need to be replicated, and the results need to be statistically validated (Kean, Downey, and Stough 2016). Of note, subjects with brain imaging performed under Bm administration showed modulatory effects of this nootropic in task-specific brain regions, including the precentral gyrus and precuneus (Neale et al. 2011).

French maritime pine bark

The standardized pycnogenol extract derived from French maritime pine bark, which is highly enriched in polyphenols, has led to significant improvements in the NCD of attention in subjects with ADHD. In a randomized, controlled trial with sixty-one children suffering from ADHD, the efficacy of pycnogenol was tested by administering 1 mg/kg/day for a 1-month period of treatment. Compared to the placebo, pycnogenol treatment significantly improved attention, visual-motor coordination and concentration and reduced hyperactivity (Trebatická et al. 2006). Unexpectedly, no positive effects were obtained with pycnogenol in adults suffering from ADHD after 3 weeks of treatment with a dose of 2.22 mg/kg/day. The authors hypothesized that pycnogenol should be administered to adult ADHD patients for longer periods of time and/or at higher doses to obtain significant positive effects (Tenenbaum et al. 2002). In a related study, a 12-month long-term period of pycnogenol treatment significantly boosted cognitive function, attention, and mental performance in adults with oxidative stress and led to a significant reduction in oxidative stress levels (Belcaro et al. 2015).

Sage

Although an improvement in attentional processes might be expected, as cholinergic systems are the primary target of the active chemicals contained in sage plants, cognitive benefits reported with sage seem to be the result of the sum of small positive and negative effects exerted by the wide range of components present in the essential oil of sage plants, mainly monoterpenoids (Kennedy et al. 2011). Sage plants display a wide range of bioactivities, such as anticholinesterase, antioxidant, anti-inflammatory, estrogenic and sedative activities (Perry et al. 2003; Tildesley et al. 2005b). In healthy subjects, a single dose of sage essential oil (50 µL) improved performance in memory and attention tasks, reduced mental fatigue and increased alertness (Kennedy et al. 2011). In patients with mild to moderate AD, sage boosted attention and reduced neuropsychiatric symptoms when taken at a dose of 60 drops/day for 16 weeks (Akhondzadeh et al. 2003; Nct 2005; Perry et al. 2003). The effect of sage on attention seems to be age-related, causing improvements in attention accuracy in healthy elderly individuals (Scholey et al. 2008) while more intensely affecting alertness, contentedness and calmness in younger subjects (Kennedy et al. 2006; Tildesley et al. 2005a).

Plant-derived nootropics and executive functions

Executive function is seen as the foundation of self-directed behavior control and is based on working memory to inhibit impulsive responses to stimuli (Shields, Moons, and Slavich 2017). This cognitive domain is mainly controlled by frontal cortical networks (Ball et al. 2011), and its proper functionality is key in problem solving, planning ahead, learning and social interaction with others and one's self; thus, this NCD is also closely related to human stress (Blair 2016; Roiland et al. 2015). Additionally, this cognitive domain is highly related to the speed of cognitive processing, such that impairments in this domain result in cognitive rigidity and perseverative behavior (Horning and Davis 2012). Nootropics commonly used and previously reviewed as memory boosters, cognition enhancers and learning capacity improvers seem effective in improving executive functions. The most commonly employed plant-derived executive function boosters include (but are not limited to) Gb, Bm and caffeine (Goel and Maurya 2019). Other nootropics with modulatory effects in this NCD are briefly reviewed in the 'Other plant-derived nootropics with modulatory effects on executive functions' section in the supplementary materials.

Ginkgo biloba

It has been widely discussed whether Gb tree leaf extracts possess the ability to improve cognition in healthy subjects, and a large number of studies have been conducted to address this hypothesis (Stough et al. 2001a). In 2006, more than 1000 clinical studies analyzing the effects of Gb extracts on cognition were evaluated, showing that the effects of Gb extracts on improving cognition were impairment-, dose- and time-dependent, with 15 days being the minimum time span required to observe therapeutic effects. From previous global and exhaustive analyses, the author concluded that cognitively impaired subjects, in particular, those with impaired executive functions, including reaction time and global functioning, performed significantly better with Gb extract administration than with placebo administration (York 2006). More recent studies have also found similar or inconclusive results regarding the actions of Gb in the NCD of executive function (Snitz et al. 2009). For example, a randomized, double-blind, placebo-controlled clinical trial that did not obtain any significant effect of Gb on global cognitive change and, more specifically, on memory, visual-spatial construction, language, attention and psychomotor speed, and executive functions was one of the largest randomized controlled trials performed to date. In this study, a dose of 240 mg of Gb (EGb 761) per day was tested in a population of 3069 community-dwelling participants, aged 72 to 96 years, with a median follow-up of 6.1 years (Snitz et al. 2009). The authors also explored the potential correlation, although nonexistent, between treatment with Gb and other factors, such as sex, age, race, education, APOE*E4 allele status, or baseline cognitive status. In 2012, a meta-analysis was also performed to collectively analyze the findings. Similarly, this study concluded that Gb did not show significant positive effects on a range of targeted cognitive functions in healthy individuals, including executive functions (Laws, Sweetnam, and Kondel 2012). Carter and colleagues hypothesized that the heterogeneity of the results may be explained by the presence of responders and nonresponders to Gb (Canter and Ernst 2003).

Gb has also been tested in humans suffering from MCI. In this specific population, Gb (LI-1370) administered twice daily (240 mg in total) for 6 months improved dual-time-related cadence, but no enhancement was observed in dual-task-related gait velocity and stride time variability (Gschwind et al. 2017). In patients diagnosed with MCI and neuropsychiatric alterations, Gb (EGb-761) improved cognition and reduced manifestations of neuropsychiatric symptoms (Gavrilova et al. 2014). In elderly women, Gb (LI-1370) improved mental flexibility, but only in those in postmenopausal Stage +2 with poorer cognitive performance (Elsabagh, Hartley, and File 2005). In relation to the effects of Gb in the context of other human diseases, one randomized, controlled clinical trial with 12 MS patients investigating the actions of Gb (EGb-761) on information processing and executive functions, aspects that are generally affected in MS, found that Gb administration showed only a moderate modulation over these aspects of cognition (Diamond et al. 2013).

In parallel, the synergetic effects of Gb combined with other nootropics have been extensively investigated based on their uses in traditional medicines. When administered together with *Panax ginseng* C.A. Mey., Gb seems to display a synergetic effect on working memory functions (Scholey, Stough, and Wesnes 2013; Wesnes et al. 2000). According to the results obtained in a double-blind, placebo-controlled, crossover trial with 24 participants, Gb, but not ginseng, improved executive function in females, but not in males, by modulating cardiovascular reactivity (Ong Lai Teik et al. 2016). The inefficiency of ginseng on cognition reported in this study may be explained by the reduced number of males recruited (8 males compared with 12 females). Additionally, the authors highlight that, based on the reduced cardiovascular response observed for the participants in the ginseng condition, participants may not experience the cognitive tasks as challenges, leading to a limited impact on the cardiovascular and hormonal systems. Additionally, no synergies were observed when combining Gb with Bm on executive function-related cognitive aspects in healthy subjects (Nathan et al. 2004).

Bacopa monnieri

Bm is one of the few herbs traditionally included in the Ayurveda pharmacopeia that is highly revered for its ability to improve cognition in healthy subjects (Nathan et al. 2004). Specifically, Bm has been prescribed in Ayurveda to improve aspects of memory, and several studies have evaluated the scientific evidence underlying these traditional claims. Using cheminformatics analysis, the potential bioactive compounds of Bm were computationally validated, identifying 52 active compounds and their associated 780 direct receptors (Jeyasri et al. 2020). From these computational analyses, multiple pharmacological bioactivities were also hypothesized for Bm bioactive compounds. In one study, it was found that a standardized Bm extract (CDRI-08; a total dose of 300 mg for 90 days) compared with a placebo significantly improved spatial memory in healthy participants (Stough et al. 2008). The authors also found that the period of administration, adherence to the treatment and dosage were fundamental aspects for observing therapeutic effects with this herb and its derivatives. These factors may collectively explain some results showing a lack of effects on executive functions by Bm in healthy subjects. Another study using a Bm extract (standardized by the Faculty of Pharmacy at Mahidol University, Thailand) was found to significantly improve cognitive processing in healthy adults. Furthermore, the authors observed cholinergic enzymatic activity suppression of acetylcholinesterase (AChE) in plasma obtained from these subjects, which indicated that Bm extracts may partially exert their nootropic functions through this mechanism of action (Peth-Nui et al., 2012). Similarly, other studies have described a synergistic effect of Bm with other nootropics and bioactive compounds targeting executive functions and neurological diseases that are associated with executive dysfunction, as detailed in a systematic review (Pase et al. 2012). Bm was

also tested in 48 patients diagnosed with MCI-AD or AD. The investigation was carried out by a randomized, double-blind, parallel-group, phase-2 single-center clinical trial in which the efficiency and safety of 300 mg of Bm taken daily for 52 weeks versus the administration of 10 mg of donepezil was investigated. Nonetheless, this phase-2 study did not show significant differences between the two conditions investigated after 1 year of treatment (Prabhakar et al. 2020).

Caffeine

Several studies have reported significant effects of caffeine on different aspects of executive function (Table 6 and Figure 2). Specifically, caffeine has been reported to improve task switching, alertness, executive control and control of inhibition (Barry et al. 2007; Tieges et al. 2006, 2007). However, the evaluation of executive functions and other frontal lobe-related cognitions is challenging, and evaluative tasks often become artificial (Soar et al. 2016). Thus, some authors have evaluated the effects of caffeine on executive functions by implementing ecologically valid tasks and adopting specific executive function task-related paradigms. These authors found that caffeine was able to improve executive functions beyond the previously encountered effects shown by classical test paradigms (Soar et al. 2016). The positive relationship that exists between caffeine consumption through beverages and the improvement in selective attention has been largely proven, as pointed out in a systematic review (Mancini et al. 2017). Very recently, in a related vein, it was demonstrated in a double-blind, within-subjects, repeated-measures design that caffeine consumption (200 mg of caffeine corresponding to approximately two espressos) improved reading skills in healthy young subjects, including the speed of processing the reading material and narrative content assimilation tasks, which are controlled by the NCD of executive function (Franceschini et al. 2020).

Limitations and influencing factors

As substances of natural origin, the study of PDNs presents various complications in the research of their effects. Examples of these difficulties are the combined effects of different molecules and variations of plants due to their growing conditions or preparation methods, among other external variables. Additionally, due to the large number of nootropics and studies reviewed in this systematic review, we did not delve into the active principles or mechanism of every PDN, although we briefly reviewed them when the mechanism of action was well established. It also needs to be noted that the studies compiled for each PDN sometimes presented relevant differences among them, and thus, the results are not fully comparable due to the use of different preparation/extraction methods, variations in dosage, and the application of different intervention designs.

It is also relevant to note that lifestyle factors such as diet, medication interactions and disease comorbidities can influence the results obtained in the studies and clinical trials that test the effectiveness of PDNs. Further studies aimed at specifically analyzing the relevance of these factors are thus required. Similarly, the attunement of neuropsychological measures requires that individual variables that might influence the obtained cognitive results be considered, such as sex, cultural background, and years of study, as these variables tend to favor the placebo effect (Snitz et al. 2009). We consider that it is also important to analyze the effects of PDNs based on the cognitive evolution/regression that occurs in the subjects throughout the entire timespan of the study at the individual level, as these may be more representative than the typically employed endpoint group measures.

Finally, due to our initial intention to focus this systematic review on the effects that potential plant-based nootropic substances may exert on each specific NCD and, based on the organization of the study that this fact required, this

Table 6. Summary of systematic reviews and clinical trials performed in humans, studying the effect of caffeine on executive function.

Study	Dose	Time	Participants	Effect	Reference
R PC	3 and 5 mg/kg body weight	Acute	18 regular coffee drinkers (18–30 years)	Reduced switch costs for both doses: improved task-switching performance by enhancing anticipatory processing such as task set updating, presumably through neurochemical effects on the dopamine system.	(Tieges et al. 2006; Tieges et al. 2007).
R DB PC	250 mg	Acute	24 university students (17–46 years, mean age 22.9 years)	Improved reaction time, processing related to response production and task performance.	(Barry et al. 2007).
R DB PC	1.8 g coffee (approx. 50 mg caffeine)	Acute	43 regular caffeine users (mean age 28.05 years)	Improved performance on planning, creative thinking, executive function (JEF(©)) event-, time- and action-based prospective memory. Decreased reaction times on the Stroop task, but no effect on Stroop interference.	(Soar et al. 2016)
DB RM	200 mg	Acute	Participants from two mechanistic studies (n = 24 and n = 53), typical young adult readers.	Improved global processing, without any effect on local information processing, alerting, spatial attention and executive or phonological functions. Faster text reading speed of meaningful sentences. Single word or pseudoword text reading was not affected.	(Franceschini et al. 2020)

R: randomized; DB: double blind; PC: Placebo controlled; RM: Repeated measures; JEF(©): the Jansari Assessment of Executive Function, which measures for eight separate aspects of executive functions, in addition to a total average score.

work was not preregistered in an official prospective register for systematic reviews. This fact may be observed as a limitation, as it might be linked to an assumption of a further risk of bias; however, to mitigate this risk, the authors performed parallel searches in the widely recognized independent scientific PubMed, Cochrane and Scopus databases and have fully disclosed the search strategies that were followed, the results that were obtained, and the inclusion and exclusion criteria that were implemented.

Conclusions

This systematic review provides a comprehensive summary of plant nootropics that have been scientifically shown to exert positive or conflicting effects on human cognitive function (Figure 2). Based on the systematic review performed here, we can conclude the following:

- Gb is the best studied PDN with regard to perceptual-motor functions and leads to improvements in disease-derived impairments in this NCD.
- Gb is a unique PDN that has the ability to improve the insidious cognitive effects of chronic tinnitus. Although considered by some authors as a viable pharmacological treatment for this disorder, we found inconclusive results, and further research on this relevant matter must be conducted.
- Bm has been identified as a nootropic with high potential of improving language comprehension and acquisition in young adults, including improvements in the learning capacity of these subjects with prolonged consumption.
- Bm is the best researched PDN with the most relevant efficacy on memory consolidation in cognitively normal subjects and in subjects suffering from cognitive impairment.
- Ashwagandha has been distinguished as the most relevant PDN based on its effects on social cognition. This herb has largely shown outstanding ability to diminish anxiety-related physiological and behavioral markers. Similarly, extracts from this herb have been used as adjuvants to pharmacological treatments in subjects with psychiatric disorders affecting social cognition.
- St. John's wort, although revered in some Western countries for its antidepressant and mood stabilizing capacities, demonstrated negative effects with regard to improvements in depression in several clinical trials. Thus, its effects on affective disorders require further research.
- Caffeine is the most relevant PDN at this time with regard to improved attention and executive function-related cognition and enhanced other NCD functions in the short term. However, this molecule possesses certain undesired effects, such as the caffeine crash, which has been proven to be ameliorated when administered in combination with *Alpinia galangal* (L.) Willd.

Ashwagandha, Bm and, to a lesser extent, Gb, were identified in this work as relevant PDNs with the abilities to exert significant effects on the NCD of attention.

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