Plant natural products for cognitive impairment: A review of the preclinical evidence

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ABSTRACT
Cognitive impairment (CI) is a highly complex central nervous system disorder commonly associated with aging. This condition is characterized by a progressive reduction of cognitive function. Modern synthetic drugs have been granted clinical approval for the treatment of CI. However, most of these drugs show insufficient efficacy and undesired side effects in clinical practice. Alternative drugs for CI are required to overcome these problems. Medicinal plants and their bioactive molecules remain the main sources for new drug discovery, and they have the potential to be developed as novel drugs for CI. Many reports have demonstrated the activity of other medicinal plants and their active metabolites for CI in various experiments. In this article, we summarize the potency of plant natural compounds for CI, focusing on cognitive-enhancing activity in amnesic-animal experimental models. We also discuss the pathophysiological basis of CI and propose potential therapeutic targets of CI using plant natural compounds. Additionally, we highlight promising natural compounds for CI and discuss their possible mechanisms of action. This review provides insight into the effort of discovery and development of pharmaceutical agents derived from medicinal plants to combat CI.

INTRODUCTION
Cognition, an exclusive function of the brain, is the sum total of mental activities involved in thinking, reasoning, learning, and memory regulation. Impairment of this function is well known as cognitive impairment (CI) disease (Deture and Dickson, 2019; Johansson et al., 2015). This condition is characterized by impairment in attention and focus, calculation ability, decision-making, thinking, and memory. CI is a complex and progressive disease caused by many factors. Many studies describe aging as a major risk factor in CI. The prevalence of CI was reported to increase linearly with increasing age (19.2% at 65–74 years old, 27.6% at 75–84 years old, and 38% at 85 years or older). There are more than 16 million people in the USA with CI, and almost 5.1 million have Alzheimer’s disease (AD), the most common type of CI. This number is predicted to be tripled or around 152 million people in 2050, especially in low- and middle-income countries (Li et al., 2020; Richardson et al., 2019).

The incidence of CI is also associated with several serious and mental diseases, such as AD (8.2%), stroke or cerebrovascular diseases (5.7%), and alcohol abuse (1.5%). The mortality rate of CI is 8%, and it tends to increase annually. Although stroke and AD are the two diseases with the fastest annual progression (20% and 17%, resp.), the annual progression of CI to dementia is still high (11.7%). In addition, CI has many negative impacts on health status, independence, and socioeconomic aspects of human beings. CI is considered as a high-cost illness from a socioeconomic perspective. Previous clinical studies in the USA reported that AD and dementia are the third most expensive diseases, costing approximately nine times more than other diseases. Globally, the costs of AD and dementia reached as much as US$ 2 trillion in 2030 (Rizzi et al., 2014). Thus, a therapeutic approach preventing or curing CI is crucial to maintain and even increase the health status of the global community. To date, the clinical effectiveness of conventional drugs for the treatment of
CI (e.g., tacrine, donepezil, rivastigmine, and galantamine) is still limited. These drugs failed to provide consistent efficacy across all cases of CI. Moreover, undesirable side effects (e.g., nausea, vomiting, hepatotoxicity, and diarrhea) often accompanied the main therapeutic effect in long-term medication (Mehta et al., 2012; Sharma et al., 2019; Tiwari et al., 2019). This emphasizes the need for discovering alternative therapeutic agents for CI with high efficacy and minimal side effects.

One of the potential sources of agents to prevent or cure neurodegenerative diseases is medicinal plants. Plants provide bioactive natural compounds with wide structural diversity that might match the therapeutic targets of CI and other neurological disorders (Lautie et al., 2020). Many studies have been conducted to explore the potential of medicinal plants for the treatment of CI using different targets and mechanisms of action. Additionally, some studies demonstrated the chemical constituents responsible for the activity of such plants and their therapeutic targets. The mechanisms underlying the pharmacological effects to explain how the phytochemical constituents exert their effects were also reported.

In this review article, we summarize the cognitive-enhancing effects of plant natural compounds from preclinical studies. The therapeutic targets or modes of action in the context of CI are also discussed in this article. To provide a scientific basis for CI therapy and a better understanding of the therapeutic targets, the pathophysiology of CI was also briefly introduced.

Pathophysiology of CI

Previous studies suggested that several abnormal conditions of the central nervous (CNS) are strongly correlated with the pathology of CI in humans (Adams et al., 2017; Mufson et al., 2012). We have summarized these with an emphasis on the four conditions explained below as a suggested model of the underlying mechanism of CI pathophysiology (Fig. 1).

Aging and CI

Aging is a natural physiological process closely related to decreased human quality of life and increased complex disease risk factors, including neurodegenerative disorders. The majority of elderly people demonstrate a decrease in the endogenous immune system and antioxidant systems. These conditions lead to inflammatory reactions, aging, and oxidative stress, which cause impairment of brain neurons (Fard and Con, 2019).

Amyloid beta (Aβ) and tau proteins in CI

Aβ plaque is a toxic protein and represents a hallmark of AD. This insoluble protein is a product of amyloid precursor protein (APP) degradation by the enzyme secretase. The three types of Aβ protein are Aβ monomer, dimer, and oligomer. Among them, the oligomer Aβ is the most toxic to the brain. The oligomer AB can reside in several regions of the brain, such as the basal ganglia, thalamus, hypothalamus, medulla oblongata, and cerebellum. Additionally, neurofibrillary tangles (NFT), a misfolded form of tau protein, are also found and can lead to CI and other brain diseases. In the normal condition, tau protein is a substantial protein that plays a role in the stabilization of the microtubules of neurons. This protein is part of the neuron and responsible for maintaining nutrients and transporting substances required by the brain. The accumulation of Aβ plaque and NFT in the temporal and frontal cortex regions leads to synaptic dysfunction and further provokes CI in the patients with AD via oxidative stress and neuroinflammatory mechanisms (Deture and...
Interestingly, drugs that antagonize ChE and NMDA are potential therapeutic targets in CI. Antioxidant, anti-inflammatory, and neurotransmitter modulator represent the promising therapeutic target of plant natural products for combating CI.

Cerebral hypoperfusion and CI
CI is commonly found in poststroke and/or traumatic brain injury conditions. Hemodynamic abnormalities, particularly in cerebral hypoperfusion, are associated with neurodegeneration in these conditions. Hypoperfusion of the cerebri causes imbalances of endogenous reactive oxygen species/nitrite oxygen species (ROS/NOS)-antioxidant systems and leads to oxidative brain injury. This condition activates microglia to release a number of proinflammatory cytokines and induces a severe neuronal loss in the brain (Liu and Zhang, 2012).

Neurotransmitter disturbances and CI
Disturbances in acetylcholine (ACh), serotonin (5HT), dopamine (DA), and glutamate (Glu) neurotransmitters contribute to memory and learning deficiencies and cause CI. Decreasing ACh, 5HT, and DA levels in the brain are closely correlated with AD and Parkinson’s disease. The low level of these neurotransmitters in the brain is caused by aberrations in their production located in the presynapse and/or by degradation in the synaptic junction. This condition interferes with the transmission of nerve impulses and impairs cognitive functional signaling pathways. In contrast to the neurotransmitters mentioned previously, high levels of Glu induce calcium neuroexcitotoxicity through persistent activation of N-methyl-d-aspartate acid (NMDA) and α-amino-3-hydroxy-5-methylisoxazole propionic acid receptors and cause neuronal damage (Yunqi et al., 2013).

Oxidative stress and neuroinflammation as a major pathogenetic mechanism of CI
Imbalances of the endogenous antioxidant system are reported as one of the major causes of progressive neurodegenerative diseases. In this case, overproduction of ROS/NOS causes oxidative stress that triggers lipid peroxidation and induces neuronal damage in the brain (Tönnes and Trushina, 2017). Neuroinflammation is the body’s response to the accumulation of Aβ plaque and is recognized as a common feature of AD. Neuroinflammation is considered as a key factor in the pathogenesis and progression of AD. Neuroinflammation is initiated by the activation of microglia, which induces the release of proinflammatory cytokines, such as IL-6 and tumor necrosis factor alpha (TNFα) (Kimney et al., 2018). An understanding of the pathophysiology of neuroinflammation is crucial for identifying potential therapeutic targets in the effort to discover and develop cognitive-enhancing drugs.

Potential therapeutic targets in CI
There are four potential therapeutic targets for the prevention and treatment of CI. These therapeutic targets are shown in Figure 2.

Neurotransmitter modulators
The common target of cognitive function-enhancing drugs is the inhibition of cholinesterase (ChE) and monoamine oxidase enzymatic activity, as well as the inhibition of the enzymes responsible for ACh and monoamine neurotransmitter degradation.

Figure 2. Potential therapeutic targets in CI. Antioxidant, anti-inflammatory, antitau, antiamyloid, and neurotransmitter modulator represent the promising therapeutic target of plant natural products for combating CI.

These so-called “neurotransmitter modulator” drugs effectively increase intracellular levels of ACh, 5HT, and DA. In memory and learning ability, neurotransmitter modulators are required to initiate neurotransmitter–receptor binding postsynapse, which stimulates various cellular and molecular signal transductions to improve cognitive function, regulation, and maintenance (Ferreira-Vieira et al., 2016; Hampel et al., 2020; Stanciu et al., 2019). Interestingly, drugs that antagonize ChE and NMDA are ineffective at stopping the progression of CI. However, the clinical use of these drugs is proven to be effective at improving cognitive performance and other symptoms of CI only for a short time period (Moss, 2020; Yaari and Ann, 2015).

Antiamyloidogenic
Antiamyloidogenic is a term to describe a group of drugs or substances that inhibit Aβ plaque formation, aggregation, and fibrillation, as well as promoting Aβ plaque degradation and clearance. Antiamyloidogenic agents act by downregulating β and γ-secretase and upregulating α-secretase enzyme activity. The decrease in Aβ plaque accumulation potentially reduces the risk of neuroinflammation, which represents the main factor causing AD. Antiamyloidogenic drugs are a relatively novel and promising approach for the treatment of AD and other forms of dementia. The development of these drugs is challenging, especially in the clinical trial stage (Yaari and Ann, 2015). Although the therapeutic approach targeting Aβ production and deposition is a promising hypothesis, none of the clinical trials so far succeeded in developing effective and safe therapeutic agents. The clinical outcome of this agent is determined by various factors that affect its efficacy and safety. These factors include the intrinsic factors such as polarity and molecular size that dictate the ability to cross the blood–brain barrier and the extrinsic factors such as the genetics of patients,
severity of illness, and neuropathology. The clinical trials of the agents targeting Aβ such as lanabecestat, semagacestat, verubecestat, atabcecestat, aducanumab, bapineuzumab, solanezumab, crenezumab, and gantenerumab have failed due to the lack of efficacy and the emergence of toxic effects (Abushakra et al., 2017; Tolar et al., 2020; Oxford et al., 2020).

**Antioxidant agents**

The consumption of dietary supplements comprising antioxidative agents is an appropriate approach to overcoming endogenous antioxidant system imbalances and/or insufficiencies. Antioxidants are required to improve the body’s defense system to prevent neuronal loss due to lipid peroxidation in the brain. They prevent the loss of neuron and synapse degeneration in the median temporal lobe, hippocampus, and cortex. Thus, decreases in neurotransmitter levels in the brain can be avoided. Intake of antioxidant compounds can protect the brain from the oxidative damage associated with AD. Antioxidants directly or indirectly inhibit ROS/NOS formation and modulate the activity and expression of endogenous antioxidants. Many studies have demonstrated that the consumption of polyphenol compounds with antioxidant activity is associated with a lower risk and slower progression of AD (Colizzi, 2019).

**Anti-inflammatory drugs**

The efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) for improving CI in AD is still a matter of debate. Preclinical evidence revealed that the use of NSAIDs is a promising therapeutic approach for the prevention and treatment of AD. As mentioned earlier, chronic neuroinflammation is a well-known attribute of AD and is involved in its pathogenesis. The underlying mechanism of this drug is related to the inhibition of neuroinflammatory progression upon the occurrence of Aβ plaques and NFT in the brain. However, the administration of anti-inflammatory drugs showed modest efficacy, and this effect is inconsistent in the clinical context. NSAIDs effectively reduce the risk of AD and dementia, but only in the early stage of the diseases (Imbimbo et al., 2010). A recent clinical investigation showed that the use of several NSAIDs, especially diclofenac, was associated with a reduction of the prevalence and progression rate of CI in AD (Imbimbo et al., 2010; Stuve et al., 2020).

**Potential natural cognitive enhancers from plants**

Medicinal plants have been used traditionally to treat cognitive-related diseases, including cognitive disorders. The long history of drug development from natural products proves that many natural compounds of plant origin have inspired the discovery of new drug entities or “lead compounds” (Achilonu and Dennis, 2015; Rahimi et al., 2010). For example, physostigmine isolated from Physostigma venenosum seeds demonstrated parasympathomimetic activity in the human CNS system. Physostigmine was the first drug candidate for the treatment of AD and parasympathetic-related diseases, such as myasthenia gravis and glaucoma. Unfortunately, this development was hampered by strong scientific evidence indicating that physostigmine has a narrow therapeutic index and a short duration of action and shows undesired side effects, such as abdominal colic, nausea, vomiting, hypersalivation, and hyperhidrosis. Later, the chemical structural modification of physostigmine resulted in the development of the new drug entities epastigmine and fenserine. Another example of a promising natural compound for the treatment of AD is galantamine, an alkaloid isolated from the bulb of Galanthus nivalis. Galantamine potently inhibited AChEI and showed efficacy against AD (Hermann, 2015; Mehta et al., 2012).

Nowadays, drug discovery efforts are drawing major attention by focusing on the identification of bioactive compounds of plant origin, including those for cognitive function-enhancing drugs (Bene et al., 2020). A cognitive function enhancer, also known as a nootropic or “smart drug,” is a synthetic and/or natural substance that is used to improve cognitive functions. This drug is widely used for the treatment of neurodegenerative diseases, and it effectively enhances cognition aspects in patients with AD and other cognitive function-related disorders affecting memory, learning ability, motivation, attention, and focus. Several natural compounds that have been tested for cognitive function-enhancing activity in an amnesic-animal model are presented in Table 1.

Table 1 shows that scopolamine-induced memory loss in rodents is the most popular bioassay used by researchers for evaluating cognitive function-enhancing effects. Scopolamine is a muscarinic receptor antagonist that acts by blocking the central cholinergic system and the nervous system. Blockade of this system leads to CI (especially in learning and memory ability), which is the hallmark of AD (Balmus and Ciobica, 2017; Blokland et al., 2016; Jivad and Rabiei, 2014; Prashar et al., 2014). Additionally, scopolamine is well known as a potent inducer of ROS/NOS in the upregulation of proinflammatory cytokines in the CNS (Haidar et al., 2016). These conditions trigger neuronal damage leading to AD. Based on the bioactive compound variability presented in Table 1, we clustered the active compounds on the basis of their chemical structure. Figure 3 shows that the chemical classes of the active compounds are very diverse, ranging from simple to complex. Interestingly, flavonoids are the most frequently reported compounds for enhancing cognitive function, followed by terpenoids and alkaloids.

A flavonoid is a secondary metabolite compound with a C6-C3-C6 backbone. Flavonoids are widely distributed in plants and have various biological activities. Although most flavonoids show antioxidant activity due to the presence of hydroxyl groups (Brodowska, 2017; Kumar and Abhay, 2013), some flavonoids (e.g., curcumin, ellagic acid, genistein, kolaflavon, luteolin, myricetin, oroxylin A, quercetin, resveratrol, trans-cinnamaldehyde, vitexin, and mangiferin) exert cholinomimetic activity and block the cholinergic system. Flavonoids reduce oxidative stress and inflammation and might thus lower the risk of memory impairment. These lines of evidence suggest that flavonoids are promising natural compounds for further development as drugs for AD. Other flavonoids, such as hesperidin, rutin, anthocyanins, naringin, and silybin, are the most reported flavonoids tested for their therapeutic value in AD using in vivo models (de Andrade Teles et al., 2018).

**Multitarget action of natural compounds for CI**

Many studies have demonstrated the multitarget actions of herbal medicines and their metabolites, which is important for drug discovery and development efforts (Bizzarri et al., 2020). A multitarget drug is a new perspective on modern
Table 1. Natural compounds with potential cognitive function-enhancing activity evaluated in amnesic-animal-models.

| Compounds          | Plant/dietary sources | Test doses | Animal models                                             | Behavioral tests | Actions                                                                 | Ref                      |
|--------------------|-----------------------|------------|-----------------------------------------------------------|-----------------|------------------------------------------------------------------------|--------------------------|
| α-Amyrin           | Angelica keiskei      | 0.5; 1; 2; 4 mg/kg/day | Scopolamine (1 mg/kg/day) induced CI in male mice         | PAT             | α-Amyrin improved memory impairment by inducing ERK and GSK-3β phosphorylation in the hippocampus. | (Park et al., 2014)      |
| α-Pinene           | Thuja orientalis      | 3; 10 mg/kg/day | Scopolamine (1 mg/kg/day) induced learning and memory impairment in C57BL/6 mice | YM, MM, PAT     | α-Pinene improved memory, learning, and cognitive function by increasing ChAT expression in the cortex and inducing enzymatic antioxidant (HO-1, manganese, and SOD) level expression in the hippocampus. | (Lee et al., 2017)       |
| β-Amyrin           | A. keiskei            | 0.5; 1; 2; 4 mg/kg/day | Scopolamine (1 mg/kg/day) induced CI in male mice         | PAT             | β-Amyrin improved memory impairment by inhibiting AChE activity and inducing ERK and GSK-3β phosphorylation in the hippocampus. | (Park et al., 2014)      |
| Acteoside          | Callicarpa dichotoma  | 0.1; 1; 2.5 mg/kg/day | Scopolamine (1 mg/kg/day) induced amnesia in male mice    | PAT, MWM        | Acteoside increased long-term and/or short-term spatial memory formation. The mechanism is unclear, but it might target the cholinergic system and act as an antioxidant. | (Lee et al., 2006)       |
| Aloe emodin        | Rheum officinale      | 25; 50; 100 mg/kg/day | Scopolamine (2 mg/kg/day) induced memory impairment in male mice | MWM             | Aloe emodin improved cognitive deficit by inhibiting AChE, TNF, and NF-κB and modulated the NFKB/NF-κB and MAPK signaling pathways. | (Tao et al., 2014)       |
| Arctigenin         | Arctium lappa         | 3 mg/kg/day | Male APP/PS1 transgenic mice as an AD model               | MWM             | Arctigenin reversed memory impairment by inhibiting Aβ42 production (by targeting BACE1 expression and enhancing Aβ clearance via AKT/mTOR signaling and AMPK/Raptor signaling pathways). | (Zhu et al., 2013)       |
| Ascorbic acid      | Fruits and vegetables | 125 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in APP/PSEN1 transgenic mice | LAT, ZM, YM, MWM | Ascorbic acid improved learning and memory impairment via a mechanism related to its antioxidant capacity and glutamatergic neurotoxicity protection activity. | (Harrison et al., 2009)  |
|                    |                       | 60; 120 mg/kg/day | Scopolamine (0.4 mg/kg/day) and diazepam (1 mg/kg/day) induced CI in young and aged Swiss mice | EPM, PAT        |                                                                      |                          |
| Berberine          | Coptis chinensis      | 100; 500 mg/kg/day | Scopolamine (1 mg/kg/day) induced amnesia in male Sprague Dawley rats | PAT, MAT        | Berberine demonstrated an anti-amnesic effect, but the mechanism remained unknown. It might target the peripheral and central cholinergic nervous systems. | (Peng et al., 1997)      |
| Crocin             | Curcus sativus        | 7.5; 15; 30 mg/kg/day | D-galactose (400 mg/kg/day) induced aging model in male Wistar rats | MWM             | Crocin enhanced spatial and learning memory functions by acting as an antagonism (decreasing CML expression) and antioxidative (decreasing MDA level) agent. It also suppressed brain inflammatory mediators (IL-1, TNF, and NF-κB) and modulated the P38/MAPK and ERK/MAPK signaling pathways. | (Heidari et al., 2017)   |
|                    | Gardenia jasminoides  |                       |                                                        |                 |                                                                      |                          |
| Cryptotanshineone  | Salvia miltiorrhiza   | 2.5; 5; 10; 20 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in male mice | PAT             | Cryptotanshineone ameliorated memory and learning deficit by inhibiting AChE activity. | (Kim et al., 2007)       |
| Curcumin           | Curcuma longa         | 200 mg/kg/day | Heavy (4 Gy carbon) ion irradiation-induced memory and learning deficit in mice | MWM             | Curcumin reversed spatial learning and memory decline by modulating brain oxidative stress (increased SOD activity and decreased MDA level) and upregulating Nrf2 protein and its downstream genes (NQO-1, HO-1, and γ-GCS) in the brain. | (Xie et al., 2014)       |
|                    |                       |                                                        |                 |                                                                      |                          |
| 15,16-Dihydroxydihydrogenolone | S. miltiorrhiza | 0.5; 1; 2; 4 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in male mice | PAT             | 15,16-Dihydroxydihydrogenolone ameliorated memory and learning deficit by inhibiting AChE activity. | (Kim et al., 2007a)      |
| Docosahexaenoic acid | Seafood and algae    | 200; 300 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in male Albino mice | MWM, EPM, LAT   | Docosahexaenoic acid enhanced spatial memory only in the scopolamine-treated group but not in the normal group. The exact mechanism of action is not yet elucidated in this study but may be related to free-radical scavenging activity. | (Soraj and Tulika, 2018) |
| Echinocystic acid  | Codonopsis lanceolata | 10; 20 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in male mice | PAT, MM, LAT    | Echinocystic acid prevented memory impairment by inhibiting AChE activity and inducing pCREB and BDNF expression. | (Kim et al., 2007a)      |
| Ellagic acid       | Berries, nuts, seeds, and vegetables | 10; 30; 100 mg/kg/day | Scopolamine (0.4 mg/kg/day) and diazepam (1 mg/kg/day) induced memory deficit in male Wistar rats and mice | EPM, LAT, PAT   | Ellagic acid prevented memory impairment by inhibiting AChE activity and promoted the antioxidative defense system (decreased MDA level and increased GSH, SOD, and catalase activity). | (Mansouri et al., 2016)  |
|                    |                       |                                                        |                 |                                                                      |                          |
|                    |                       | 25; 50 mg/kg/day | Scopolamine (0.7 mg/kg/day) induced Alzheimer’s type memory and cognitive dysfunction in male Wistar rats | EPM, LAT        |                                                                      | (Kaur and Mehan, 2015)   |

(Continued)
| Compounds          | Plant/dietary sources | Test doses          | Animal models                                                                 | Behavioral tests | Actions                                                                                                   | Ref               |
|--------------------|-----------------------|---------------------|-------------------------------------------------------------------------------|------------------|--------------------------------------------------------------------------------------------------------|-------------------|
| Erucic acid        | Raphanus sativus      | 1; 3; 10 mg/kg/day | Scopolamine (1 mg/kg/day) induced CI in male mice                             | PAT, YM, MWM     | Erucic acid enhanced memory performance by increasing PI3K, PKC, ERK, CREB, and AKT phosphorylation levels. | (Kim et al., 2016a) |
| Ferulic acid       | Allium tuberosum      | 0.002%; 0.005% (w/v) | TMT (2.5 mg/kg/day) induced cognitive deficit in male mice                   | PAT, YM          | Ferulic acid prevented cognitive dysfunction by activating ChAT activity in the brain.                  | (Kim et al., 2007b) |
| Forsythiaside      | Forsythia suspensa    | 2.5; 5; 10; 20 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in male mice             | PAT, MWM         | Forsythiaside enhanced learning and memory performance by protecting the brain from lipid peroxidation. | (Kim et al., 2009a) |
| Flos lonicerae     | Fruit cornus          | 20; 40 mg/kg/day   | Scopolamine (0.5 mg/kg/day) induced amnesia in male mice                      | OFT, OLRT, MWM   | Genistein enhanced memory by promoting cholinergic neurotransmission (decreasing AChE activity and increasing ChAT activity and ACh levels) and by enhancing antioxidative capacity (increasing SOD activity and GSH content and decreasing MDA levels). It also induced the ERK/CREB/BDNF signaling pathway in the hippocampus. | (Lu et al., 2018) |
| Ginsenoside Rg5    | Panax ginseng         | 5; 10; 20 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory deficit in male mice                | PAT, YM, MWM     | Ginsenoside Rg5 and Rh3 inhibited AChE activity and increased CREB activation and BDNF expression, to improve memory impairment. | (Kim et al., 2013) |
| Ginsenoside Rh3    | Panax ginseng         | 5; 10; 20 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory deficit in male mice                | PAT, YM, MWM     | Ginsenoside Rg5 and Rh3 inhibited AChE activity and increased CREB activation and BDNF expression, to improve memory impairment. | (Kim et al., 2013) |
| Gintonin           | Glycine max (soybean) | 10; 20; 40 mg/kg/day | Scopolamine (0.75 mg/kg/day) induced amnesia in male mice                    | PAT, YM, MWM     | Gintonin reversed memory and cholinergic impairments by acting as a lyophosphatidic acid (LPA) receptor ligand to increase ACh release and ChAT expression in hippocampus. | (Kim et al., 2015) |
| Gluco-obtusifolin  | Cassia obtusifolia    | 0.5; 1; 2; 4 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in male mice            | PAT, MWM         | Gluco-obtusifolin reversed memory impairment by acting as an AChE inhibitor.                            | (Dong et al., 2009b) |
| Gomisin A          | Schizandra chinesis   | 2.5; 5; 10; 20 mg/kg/day | Scopolamine (1 mg/kg/day) induced memory impairment in male mice            | PAT, YM, MWM     | Gomisin A improved spatial long-term and short-term memory by inhibiting AChE activity.                   | (Kim et al., 2006) |
| Gypenoside TN-2    | Gynostemma pentaphyllum | 10; 20; 40 mg/kg/day | Scopolamine (0.9 mg/kg/day) induced learning deficit in male mice         | PAT, YM, MWM     | Gypenoside TN-2 inhibited memory and learning impairment by activating the CREB/BDNF signaling pathways. | (Hong et al., 2011) |
| Harmine            | Peganum harmala       | 20 mg/kg/day       | Scopolamine (1 mg/kg/day) induced memory impairment in male mice            | MWM              | Harmine enhanced spatial cognition and reversed memory impairment by inhibiting AChE activity and inducing Egr-1, c-Fos, and c-Jun expression. | (He et al., 2015) |
| Huperzine A        | Huperzia serrata      | 0.14 mg/kg/day     | Scopolamine (1.5 mg/kg/day) induced amnesia in male Sprague Dawley rats   | MWM              | Huperzine A enhanced spatial learning and memory ability by inhibiting AChE activity and modulating oxidative stress damage (increasing SOD and GSH-Px activities and decreasing MDA levels) in the hippocampus and cerebral cortex. | (Shi et al., 2010) |
| Imperatorin        | Angelica archangelica | 1; 5; 10 mg/kg/day | Scopolamine (1 mg/kg/day) induced CI and oxidative stress in naive male Swiss mice | PAT, LAT         | Imperatorin improved memory performance by increasing enzymatic antioxidant (SOD and GSH-Px) activity and decreasing lipid peroxidation (MDA) levels in the cortex and hippocampus. | (Budzynska et al., 2015) |
| Kolaviron          | Garcinia kola         | 25; 50; 100 mg/kg/day | Scopolamine (3 mg/kg) induced memory impairment in male Albino rats        | YM, MWM          | Kolaviron improved short- and long-term memory by inhibiting AChE, decreasing oxidative stress (reducing nitrite and MDA levels), and increasing antioxidant capacity (increasing GSH-Px and SOD levels) in the hippocampus, stratum, and prefrontal cortex. | (Isbola et al., 2017) |
| Lancemaside A      | C. lanceolata         | 10; 20 mg/kg/day   | Scopolamine (1 mg/kg/day) induced memory impairment in male mice            | PAT, YM, MWM     | Lancemaside A reversed memory and learning impairment condition via AChE activity inhibition and CREB/BDNF signaling pathway modulation. | (Jung et al., 2012) |
| Lisistrazine Phosphate | Ligusticum chuanxiong | 110 mg/kg/day      | Scopolamine (1.5 mg/kg/day) induced amnesia in male Sprague Dawley rats | MWM              | Lisistrazine phosphate enhanced spatial learning and memory ability by inhibiting AChE activity and modulating oxidative stress damage (increased SOD and GSH-Px activities and decreased MDA levels) in the hippocampus and cerebral cortex. | (Shi et al., 2010) |
| Loganin            | Flos lonicerae        | 20; 40 mg/kg/day   | Scopolamine (0.5 mg/kg/day) induced memory impairment in male mice         | YM, PAT, MWM     | Loganin reversed memory impairment by inhibiting AChE activity in the hippocampus and frontal cortex.    | (Kwon et al., 2009) |
| Compounds               | Plant/dietary sources                        | Test doses (mg/kg/day) | Animal models                  | Behavioral tests | Actions                                                                 | Ref                  |
|-------------------------|---------------------------------------------|------------------------|--------------------------------|------------------|--------------------------------------------------------------------------|----------------------|
| Luteolin                | Chrysanthemum morifolium                   | 10; 20; 40             | Streptozotocin (3 mg/kg/day)   | MWM              | Luteolin improved spatial learning and memory; it also increased the thickness of the CA1 pyramidal layer structure. The exact mode of action is not known, but it might be associated with its antioxidative effect. | (Wang et al., 2016) |
| Mangiferin              | Anemarrhena asphodeloides                  | 10; 20; 40; 50         | Scopolamine (1 mg/kg/day)      | PAT, MWM         | Mangiferin improved long-term cholinergic memory by inhibiting AChE activity and proinflammatory cytokines (TNFα and NFκB) in BV-2 microglial cells. | (Jung et al., 2009) |
| Myricetin               | Berries, vegetables                        | 25; 50; 10             | Scopolamine (0.2 mg/kg/day)    | MWM              | Myricetin improved spatial learning and memory via AChE activity inhibition and brain iron level downregulation. It also protected the brain from oxidative damage. | (Wang et al., 2017) |
| Nodakenin               | Angelica gigas                             | 2.5; 5; 10; 20         | Scopolamine (1 mg/kg/day)      | PAT, YM, MWM     | Nodakenin ameliorated spatial long-term and working memory dysfunction by inhibiting AChE activity in the cholinergic signaling pathway. | (Kim et al., 2007c) |
| Obtusifolin             | C. obtusifolia                             | 0.25; 0.5; 1; 2        | Scopolamine (1 mg/kg/day)      | PAT, YM          | Obtusifolin reversed memory impairment by acting as an AChE inhibitor. | (Kim et al., 2009b) |
| Oroxyl A                | Scutellaria baicalensis                    | 2.5; 5; 10             | Scopolamine (1 mg/kg)          | PAT, YM, MWM     | Oroxyl A improved CI by acting as a GABA receptor antagonist.           | (Kim et al., 2007d) |
| Paeoniflorin            | Paeonia lactiflora                        | 40                     | Vascular dementia in male      | MWM              | Paeoniflorin reversed memory impairment and inhibited and reduced cerebral hyperperfusion and hippocampal morphological-ultrastructural changes by decreasing proinflammatory cytokine expression (IL-1β, IL-6, TNF-α, and NO) via mTOR/NFκB signaling pathway inhibition, increasing anti-inflammatory cytokines (IL-10, TGFB-β1) via P38/akt signaling pathway activation, and also activating cannabinoid receptor 2 in the hippocampus. | (Ohta et al., 1993) |
| Palmatine               | Coptidis rhizoma                          | 0.1; 0.5; 1            | Scopolamine (0.4 mg/kg) and    | EPM, MWM         | Palmatine enhanced memory by acting as an AChE inhibitor and interacted with the GABA-benzodiazepine pathway. It also acted as an antioxidative agent. | (Dhingra and Kumar, 2012) |
| Phytoceramide           | Sweet potatoes, rice bran, and wheat       | 5; 10; 20; 50          | Scopolamine (1 mg/kg/day)      | PAT, YM          | Phytoceramide increased cognitive performance and neurogenesis in the hippocampal dentate gyrus regions via CREB/BDNF signaling pathway activation. | (Lee et al., 2013) |
| Polygalacic acid        | P. tenuifolia                             | 3; 6; 12               | Scopolamine (1 mg/kg/day)      | MWM              | Polygalacic acid reversed CI by modulating cholinergic systems (decreased AChE activity, increased ChAT activity, and ACh levels) in the hippocampus and frontal cortex. It also showed anti-inflammatory activity (attenuated IL-1β and enhanced IL-10) and demonstrated antioxidative effects (increased SOD activity, decreased MDA, and GSH levels) in the brain. | (Guo et al., 2016) |
| Pseudoginsenoside-F1    | Panax quinquefolium                       | 1.6; 8                 | Aβ1-42 (410 pmol) induced AD  | MWM, PAT         | Pseudoginsenoside-F1 improved behavioral performance and inhibited APP as well as Aβ1-42 production via oxidative stress modulation (increased SOD and GSH-Px activities and decreased MDA levels). It also interfered with apoptosis pathways (decreased JNK2, p53, and cleaved caspase 3 expression) in the cortex and hippocampus. | (Wang et al., 2013) |
| Quercetine              | Vegetables, fruits, e.g., onions, potatoes, cabbages, lettuces, apples, mangoes, and black currants | 50; 75; 100            | D-galactose (50 mg/kg/day)     | MWM              | Quercetine improved exploratory behavior, spatial learning, and memory via oxidative stress prevention (decreased *OH levels and increased GSH content) in the hippocampus and cerebral cortex. | (Liu et al., 2006) |
| Resveratrol             | Grapes                                    | 12.5; 25; 50           | Scopolamine (0.6 mg/kg/day)    | PAT, MWM, LAT    | Resveratrol improved learning and memory performance in scopolamine-induced rats but not in mecamylamine-induced rats. The mode of action might target the muscarinic system rather than the nicotinic system. | (Giacar et al., 2011) |
|                         |                                           | 10; 20; 40             | Aβ1-42 (0.4 μg/ side CA1) induced memory impairment in male mice | MWM, PAT         | Resveratrol ameliorated learning and memory impairment by activating PDE4-related signaling (decreased PDE4 expression and upregulated pCREB and BDNF expression), decreasing proinflammatory cytokines (IL-6 and IL-1β), and regulating apoptotic proteins expression (increased Bcl2 and decreased Bax) in the hippocampus. | (Wang et al., 2016) |
drug design, especially for combating complex diseases, including neurodegenerative diseases (AD, Parkinson’s disease, schizophrenia, and depression) and cancers. These diseases have multiple pathophysiological and pathological aspects manifested in their clinical symptoms. Therefore, a single target drug might be inadequate to effectively achieve the therapeutic goal (Ramsay et al., 2018). Consequently, an effective drug might be developed on the basis of multiple targets to cover complex therapeutic targets.

As a recent study indicated that CI is a complex disease involving genetic, environmental, and aging factors with...
complicated pathophysiology (Alber, 2017; Sun et al., 2017; Tiwari et al., 2019), a multitarget approach is needed for the development of CI drugs. In this regard, plant natural compounds represent a potential source. Plants serve compound diversity that is historically proven to inspire drug discovery and traditionally used for medicinal purposes in various diseases, including complex ones (Benek et al., 2020; Chen and Decker, 2013).

As previously shown in Table 1, many plant-derived natural compounds exhibited cognitive-enhancing activity in amnesic-animal models. Their potential effects were evaluated by behavioral testing, employing short and/or long-term spatial and working memory performance evaluations. Memory is an important factor in cognition function, and impairment of cognitive function is associated with the early stage of cognitive problems (Robertson, 2002). Based on Table 1, plant natural compounds were grouped on the basis of their mechanisms of action (Fig. 4). Figure 4 shows that the cholinergic nervous system is the major target of the majority of the potential natural compounds, followed by ROS/NOS and some of the signaling pathways in the CNS for their activity.

Fifteen compounds showed multitarget action, by at least three different mechanisms. These compounds were gintonin, thymoquinone, huperzine A, aloe emodin, curcumin, ellagic acid, genistein, kolaviron, resveratrol, stevioside, schisandrin B, sulforaphane, echinocystic acid, lancemaside A, and polygalactic acid, and they have a high potential to be further developed as
drugs targeting CI. Polygalacic acid and genistein are the most potential and promising candidates as a new cognitive function-enhancing drug. These compounds can be found in Polygala tenuifolia and Glycine max (soybean). Polygalacic acid (3; 6; 12 mg/kg; p.o) and genistein (10; 20; 40 mg/kg and 10; 20; 40 mg/kg; p.o) were able to inhibit memory impairment in mice induced by scopolamine. Polygalacic acid and genistein showed a synergistic effect in targeting CI. These compounds have several mechanisms (i.e., regulating the cholinergic nervous system, activating the extracellular signal-regulated kinase (ERK)/cAMP response element binding (CREB)/brain-derived neurotrophic factor (BDNF) signaling pathway, and protecting the hippocampus and frontal cortex from oxidative and inflammatory stresses). The activity of polygalacic acid and genistein is of note, as it protects the hippocampus and frontal cortex (the most important regions of CNS for cognition regulation) from injuries and stresses. However, further studies are required to clarify their anti-amnesic activity in human using clinical trials (Guo et al., 2016; Lu et al., 2018).

The limitations of natural cognitive enhancers from plants

Plant natural compounds have a potential to be developed as a cognitive-enhancing agent. They provide a huge chemical diversity and might offer an alternative therapeutic approach. On the contrary, plant natural compounds have some limitations that restrict their development as a drug. Several clinical evidences indicated that herbal medicines and their metabolite constituents demonstrated inconsistent clinical outcomes. This due to the unclear pharmacokinetic aspect of the active compound, poor bioavailability, and lack of penetration across the blood-brain barrier. Consequently, these compounds failed to achieve the minimum therapeutic concentration in CNS, leading to the lack of efficacy. In addition, variability in the quality of plant raw material, harvesting process, extraction method, and production process also affect the quality of the final product (Kunle et al., 2012; Ratheesh et al., 2017).

CONCLUSION

Many studies showed that plant natural compounds have a positive influence on cognitive performance in animal experimental models. These compounds were able to improve cognitive functions and to enhance short/long-term spatial and working memories. Based on the current literature, we identified 15 plant natural compounds that showed multitarget action for combating CI. Polygalacic acid and genistein are among the most promising of these compounds, as they are able to interact with multiple molecular targets related to CI and are considered as promising lead compounds for drug development and dietary supplementation in the treatment of CI.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in this work.

ETHICAL APPROVAL

This study does not involve the use of animals or human subjects.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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