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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

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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

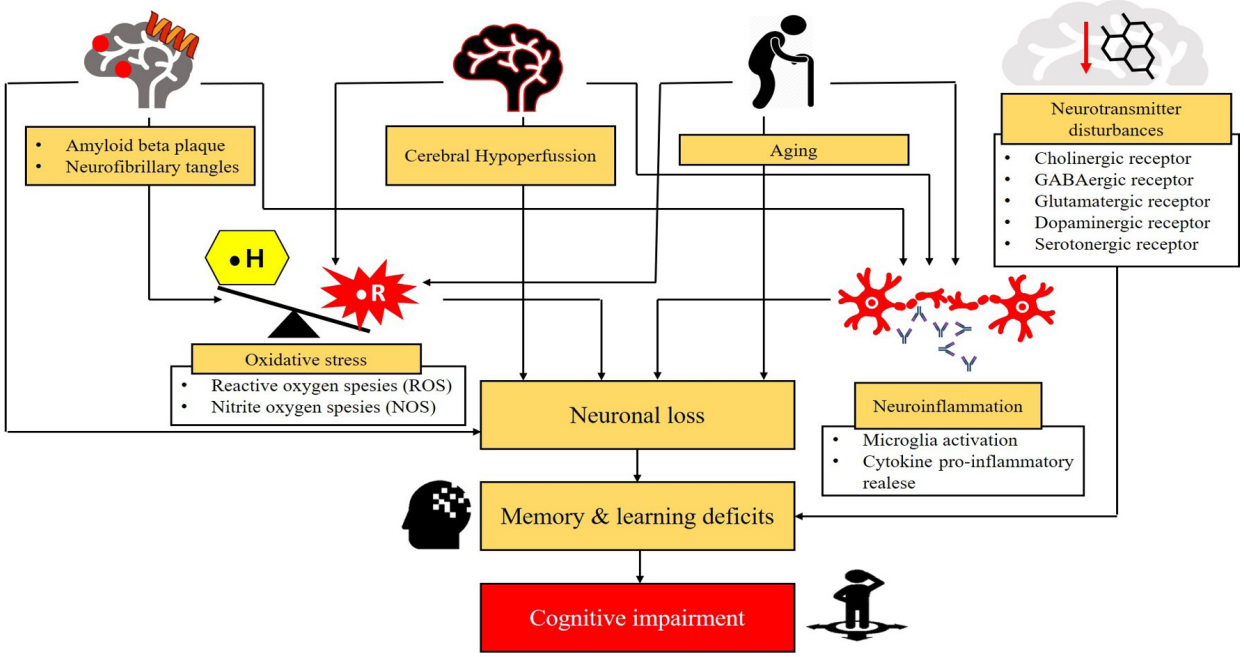

Figure 1. Pathophysiology of CI. Oxidative stress and neuroinflammation are the two main events leading to CI. The other factors associated with the pathophysiology of CI are the presence of Aβ and tau protein, cerebral hyperperfusion, aging, and neurotransmitter disturbances. These factors lead to neural loss and memory/learning deficits leading to CI.

Dickson, 2019; Tönnies *et al*., 2017; Kent *et al*., 2020; Tiwari *et al*., 2019).

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 (Tönnies 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) (Kinney *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.

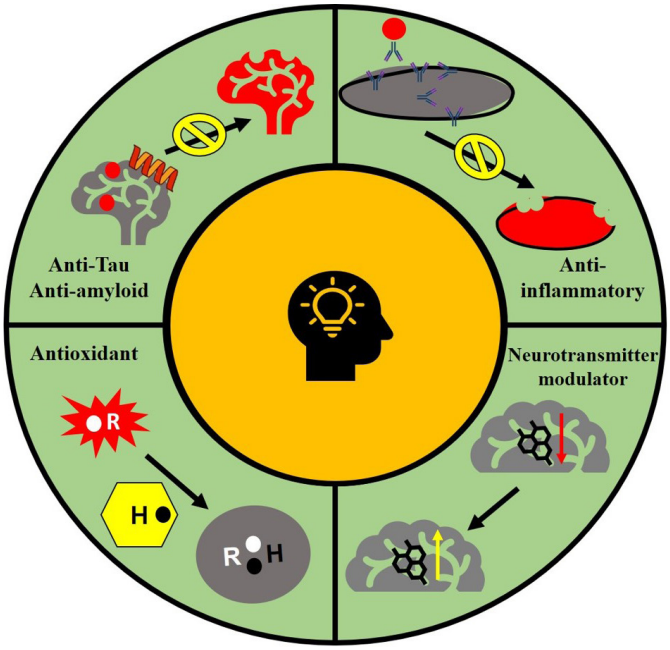

Figure 2. Potential therapeutic targets in CI. Antioxidant, anti-inflammatory, antitau, antiamyloid, and neurotransmitter modulator represent the promising therapeutic target of plant natural products for combating CI.

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, atabecestat, 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 (Benek *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 (Haider *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, kolaviron, 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 silibinin, 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, MWM, 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 activity and modulating oxidative stress conditions (increasing SOD and GSH-Px activities and decreasing the MDA level) in the hippocampus.	(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 Aβ 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		(Parle and Dinesh, 2003)
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 antiamnesic effect, but the mechanism remained unknown. It might target the peripheral and central cholinergic nervous systems.	(Peng *et al*., 1997)
Crocin	*Crocus sativus* *Gardenia jasminoides*	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 antiglycation (decreasing CML expression) and antioxidative (decreasing MDA level) agent. It also suppressed brain inflammatory mediators (IL-1, TNF, and NF-$_{\kappa}$B) and modulated the PI3K/AKT and ERK/MAPK signaling pathways.	(Heidari *et al*., 2017)
Cryptotanshinone	*Salvia miltiorrhiza*	2.5; 5; 10; 20 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment in male mice	PAT	Cryptotanshinone 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-Dihydrotanshinone I	*S. miltiorrhiza*	0.5; 1; 2; 4 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment in male mice	PAT	15,16-Dihydrotanshinone I 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,	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.	(Saroj and Tulika, 2018)
Echinocystic acid	*Codonopsis lanceolata*	10; 20 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment in male mice	PAT, YM, MWM	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, OFT, 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, MWM, 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 suspense*	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)
Genistein	*Glycine max* (soybean)	10; 20; 40 mg/kg/day	Scopolamine (0.75 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 **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		25; 50; 100 mg/kg/day	Scopolamine (0.5 mg/kg/day) induced memory impairment in male C57BL/6 mice	PAT, MWM	Gintonin reversed memory and cholinergic impairments by acting as lysophosphatidic acid (LPA) receptor ligand to increase ACh release and ChAT expression in hippocampus.	(Kim *et al*., 2015)
		25; 50 mg/kg/day	Amyloid-β protein (400 pmol) induced cholinergic dysfunction in male C57BL/6			
			Male APP and PSEN-1 transgenic mice as an AD model			
		50 mg/kg/day	Normal (not treated) male mice	CFCT	Gintonin enhanced memory by increasing pCREB and BDNF expression.	(Kim *et al*., 2016b)
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 C57BL/6 mice and male APP/PS1 transgenic 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 dahurica* *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.	(Ishola *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)
Ligustrazine Phosphate	*Ligusticum chuanxiong*	110 mg/kg/day	Scopolamine (1.5 mg/kg/day) induced amnesia in male Sprague Dawley rats	MWM	Ligustrazine 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* *Fruit cornus* *Strychonos nux vomica*	20; 40 mg/kg/day	Scopolamine (0.5 mg/kg/day) induced memory impairment	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	Animal models	Behavioral tests	Actions	Ref
Luteolin	*Chrysanthemum morifolium*	10; 20 mg/kg/day	Streptozotocin (3 mg/kg/day) induced AD in male Wistar rats	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	*Annemarrhena asphodeloides*	10; 20 mg/kg/day	Scopolamine (1 mg/kg/day) induced learning deficit in male mice	PAT, MWM	Mangiferin improved long-term cholinergic memory by inhibiting AChE activity and proinflammatory cytokines (TNF α and NF-$_{κ}$B) in BV-2 microglial cells.	(Jung *et al*., 2009)
Myricetin	Berries, vegetables	25; 50 mg/kg/day	Scopolamine (0.2 mg/kg/day) supplemented with a high iron dose (75 mg/kg/day) induced memory impairment in male mice	MWM	Myricetin increased 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 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory disruption in male mice	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 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment in male mice	PAT, MWM	Obtusifolin reversed memory impairment by acting as an AChE inhibitor.	(Kim *et al*., 2009b)
Oroxylin A	*Scutellaria baicalensis*	2.5; 5; 10; 20 mg/kg/day	Scopolamine (1 mg/kg) or diazepam (1 mg/kg) induced memory impairment in male mice	PAT, YM, MWM	Oroxylin A improved CI by acting as a GABA$_{A}$ receptor antagonist.	(Kim *et al*., 2007d)
Paeoniflorin	*Paeonia lactiflora*	40 mg/kg/day	Vascular dementia in male Sprague Dawley rats	MWM	Paeoniflorin reversed memory impairment and inhibited and reduced cerebral hypoperfusion and hippocampal morphological-ultrastructural changes by decreasing proinflammatory cytokine expression (IL-1β, IL-6, TNF-α, and NO) via mTOR/NF-$_{κ}$B signaling pathway inhibition, increasing anti-inflammatory cytokines (IL-10, TGF-β1) via PI3K/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 mg/kg/day	Scopolamine (0.4 mg/kg) and diazepam (1 mg/kg) induced amnesia in Swiss-Albino male mice	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 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory deficit in male mice	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 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory deficit in male mice	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-β and enhanced IL-10) and demonstrated antioxidative effects (increased SOD activity, decreased MDA, and GSH levels) in the brain.	(Guo *et al*., 2016)
Pseudoginsenoside-F$_{11}$	*Panax quinquefolium*	1.6; 8 mg/kg/day	Aβ$_{1–42}$ (410 pmol) induced AD in male mice and not treated APP/PS1 mice	MWM, PAT	Pseudoginsenoside-F$_{11}$ improved behavioral performance and inhibited APP as well as Aβ$_{1–42}$ 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 mg/kg/day	D-galactose (50 mg/kg/day) induced memory impairment-aging model in male mice	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 mg/kg/day	Scopolamine (0.6 mg/kg/day) and mecamylamine (10 mg/kg/day) induced memory impairment in male Wistar rats	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.	(Gacar *et al*., 2011)
		10; 20; 40 mg/kg/day	Aβ$_{1–42}$ (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-β), and regulating apoptotic proteins expression (increased Bcl2 and decreased Bax) in the hippocampus.	(Wang *et al*., 2016)

Compounds	Plant/dietary sources	Test doses	Animal models	Behavioral tests	Actions	Ref
Rosmarinic acid	*Boraginaceae*	1; 2; 4; 8 mg/kg/day	Normal (not treated) male mice	MWM	Rosmarinic acid enhanced spatial long-term memory by inhibiting POP activity.	(Park *et al*., 2010)
Schisandrin B	*Schisandra chinensis*	10; 25; 50 mg/kg/day	Scopolamine (1 mg/kg) induced memory deficit in male Balb-c mice	PAT, MWM	Schisandrin B prevented learning and memory impairment via AChE inhibition and antioxidant status regulation (decreased nitrite and MDA levels and increased GSH, GSH-Px, and SOD levels) in the brain.	(Giridharan *et al*., 2011)
Stevioside	*Stevia rebaudiana*	250 mg/kg/day	Scopolamine (0.5 mg/kg/day) induced memory impairment in Wistar rats	MWM	Stevioside improved learning and memory performance by inhibiting AChE activity and acted as an antioxidant (decreased TBARS level and increased GSH content) in the brain.	(Sharma *et al*., 2010)
Stigmasterol	Soybean, Calabar bean, and rapeseed	2.5; 5; 10; 20 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment in male mice	PAT, MWM	Stigmasterol counteracted memory impairment by increasing pERK and pCREB expression levels in the hippocampus.	(Park *et al*., 2012)
Sulforaphane	Cruciferous vegetables e.g., broccoli, cabbage, watercress, and Brussels sprouts	10; 50 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment in female C57BL/6 mice	MWM	Sulforaphane improved memory and learning ability via cholinergic system modulation (increased ACh level and ChAT expression and decreased AChE activity) in the hippocampus and frontal cortex.	(Lee *et al*., 2014)
Tanshinone I	*S. miltiorrhiza*	0.5; 1; 2; 4 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment in male mice	PAT	Tanshinone I and II A ameliorated memory and learning abnormalities by inhibiting AChE activity.	(Kim *et al*., 2007e)
Tanshinone II A		2.5; 5; 10; 20 mg/kg/day				
Thymoquinone	*Nigella sativa*	2.5; 5; 10 mg/kg/day	D-galactose (400 mg/kg/day) induced aging and memory impairment in male Wistar rats	MWM	Thymoquinone improved memory deficit by preventing oxidative stress and neuroinflammation in the hippocampus (increased GSH, reduced MDA level, and reduced proteins level of TNF-α, IL-1β, AGEs, and GFAP).	(Oskouei *et al*., 2020)
		20 mg/kg/day	$A\beta_{1-42}$ (300 pmol) induced AD in female Sprague Dawley rats	MWM	Thymoquinone enhanced spatial memory by acting as anti-inflammatory (decreased IFN-γ) and neurogenesis inducer (increased DCX expression) in hippocampus.	(Elibol *et al*., 2019)
			Streptozotocin (3 mg/kg) induced memory deficit in female Sprague Dawley rats	MWM, PAT	Thymoquinone increased regeneration of neuron through MAPK pathways by activating JNK1/2, upregulating mir124, and downregulating and ERK1/2 and iNOS enzyme in hippocampus.	(Dalli *et al*., 2018)
Trans-cinnamaldehyde	*Cinnamomum cassia*	12.5; 25; 50 mg/kg/day	Lipopolysaccharide (0.33 mg/kg/day) induced memory impairment in male mice	OFT, NOR, MWM	Trans-cinnamaldehyde alleviated memory deficit and improved synaptic plasticity by reducing neuroinflammation markers (iNOS and IL-1β) in the microglia and inhibiting the MEK1/2-ERK1/2 signaling pathway in the hippocampus.	(Zhang *et al*., 2016)
Vitexin	*Vitex agnuscastus*	25; 50; 100 µM (i.c.v)	Scopolamine (10 µg/day i.c.v.) induced memory impairment in male Wistar rats	PAT	Vitexin improved memory retrieval by directly interacting with cholinergic and/or GABAergic receptors.	(Abbasi *et al*., 2013)
Zerumbone	*Zingiber zerumbet*	1; 10 mg/kg/day	Scopolamine (20 mg/kg/day) induced dementia and anxiety-like behaviors in Sprague Dawley rats	OFT, EPM, MWM	Zerumbone reversed anxiety and depression-like behaviors and inhibited memory impairment. The mode of action is unknown but might be related to the $GABA_A$ receptor.	(Jafarian *et al*., 2019)
Z-Ligustilide	*A. gigas* *L. chuanxiong*	2.5; 10; 40 mg/kg/day	Scopolamine (2 mg/kg/day) induced memory impairment in SPF male mice	MWM, YM	Z-Ligustilide enhanced spatial long-term and short-term memory by stimulating the cholinergic system (decreased AChE activity and increased ChAT activity).	(Cheng *et al*., 2011)

γ-GCS = gamma-glutamyl cysteine synthetase; Aβ = amyloid beta; Ach = acetylcholine; AChE = acetylcholinesterase; AGEs = advanced glycation end products; AKT = protein kinase B; AMPK = AMP-activated protein kinase; APP = amyloid precursor protein; BACE1 = beta-secretase 1; Bax = Bcl 2-associated X protein; Bcl2 = B-cell lymphoma 2; BDNF = brain- derived neurotrophic factor; CA1 = *Cornu ammonis* 1; CFCT = contextual fear-conditioning task; ChAT = choline acetyltransferase; CML = carboxymethyl-lysine; CREB = cAMP response element binding; DCX = double cortin; Egr-1 = early growth response 1; EPM = elevated plus maze; ERK = extracellular signal-regulated kinase; GABA = γ-amino butyric acid; GFAP = glial fibrillary acidic protein; GSH = glutathione; GSH-Px = glutathione peroxidase; GSK-3β = glycogen synthase kinase 3 beta; HO-1 = heme oxygenase 1; IL = interleukin; i.c.v. = intracerebroventricular injection; INF-γ = interferon-gamma; iNOS = inducible nitric oxide synthase; JNK = c-Jun N-terminal kinase; LAT = locomotor activity test; MAPK = mitogen-activated protein kinase; MAT = motor activity test; MDA = malondialdehyde; MEK = MAPK/ERK kinase; mir = microRNA; mTOR = mammalian target of rapamycin; MWM = Morris water maze; $NF\text{-}_KB$ = nuclear factor kappa-light-chain-enhancer of activated B cells; NO = nitrite oxide; NOR = novel object recognition test; NQO-1 = NADPH quinone dehydrogenase 1; Nrf-2 = nuclear factor erythroid 2-related factor 2; OFT = open field test; *OH = hydroxyl radical; OLRT = object location recognition test; p53 = tumor protein p53; PAT = passive avoidance test; pCREB = phosphorylated-CREB; PDE4 = phosphodiesterase 4; pERK = phosphorylated-ERK; PI3K = phosphoinositide 3-kinase; PKC = protein kinase C; POP = prolyl oligopeptidase; SOD = superoxide dismutase; TBARS = thiobarbituric acid-reactive substances; TGFβ = tumor growth factor beta; TNFα = tumor necrosis factor alpha; YM = Y-maze; ZM = zero maze.

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

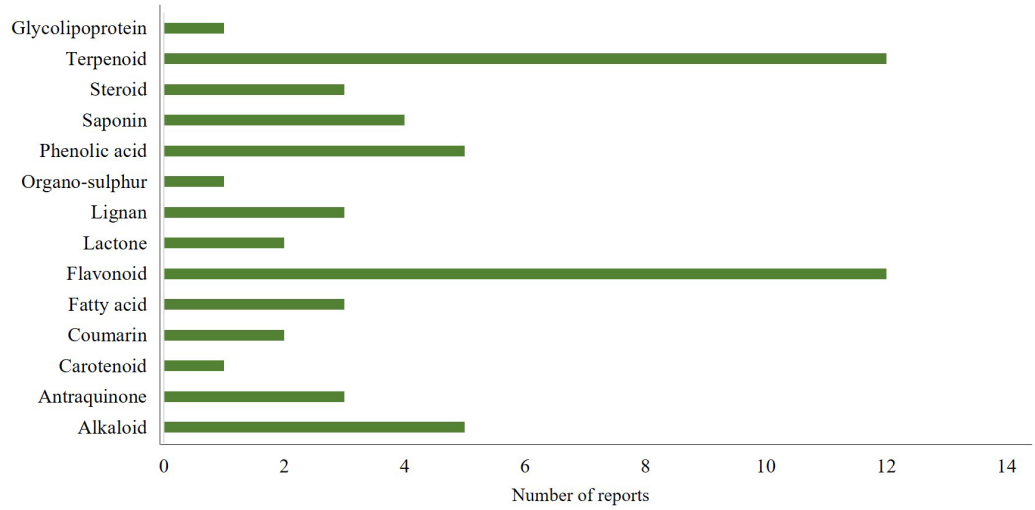

Figure 3. Chemical classes of compounds acting as memory enhancers in animal studies published from 2003 to 2020. Among the group of compounds, flavonoid and terpenoid are the most frequently reported memory enhancers, whereas only little data are available for carotenoid and organosulfur compounds.

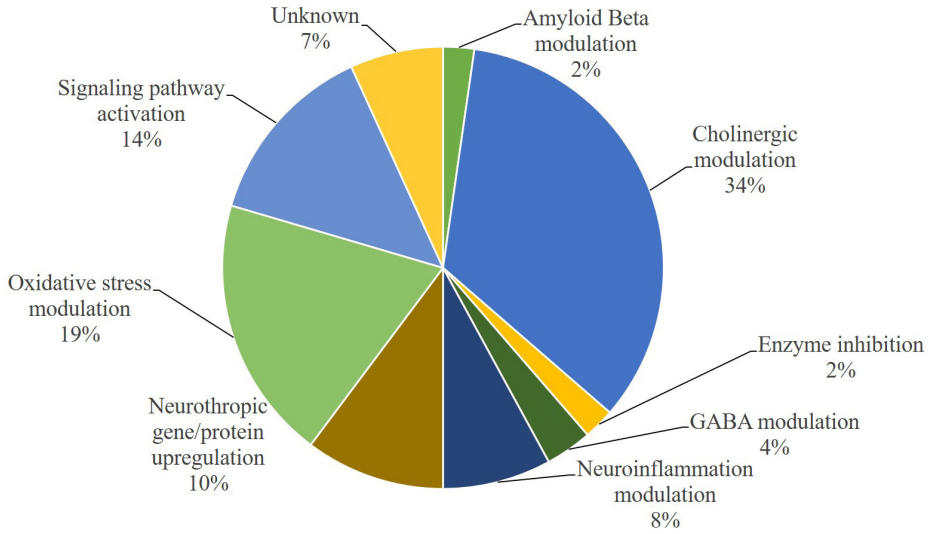

Figure 4. Comparison of the mechanism of action of plant natural products acting as cognitive enhancers evaluated in animal models. Modulation of cholinergic activity accounted for 34% of the mechanism, whereas oxidative stress modulation and signaling pathway activation accounted for 19% and 14%, respectively. The other mechanism of actions was accounted less than 10%.

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 polygalacic 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 antiamnesic 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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GRAPHICAL ABSTRACT