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 cognitive impairment 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	*Angelica keiskei*	0.5; 1; 2; 4 mg/kg/day	Scopolamine (1 mg/kg/day) induced cognitive impairment 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 Alzheimer's disease 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	EPM, PAT		(Parle and Dhingra, 2003)

			cognitive impairment in young and aged Swiss mice			
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-KB) 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	*Salvia 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., 2007)
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.	(Jung et al., 2012)
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	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	(Mansouri et al., 2016)

			and mice		activity).	
		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 et al, 2015)
Erucic acid	*Raphanus sativus*	1; 3; 10 mg/kg/day	Scopolamine (1 mg/kg/day) induced cognitive impairment in male mice	PAT, YM, MWM	Erucic acid enhanced memory performance by increasing PI3K, PKC, ERK, CREB, and AKT phosphorylation levels.	(Kim et al., 2016)
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., 2007)
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., 2009)
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	*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						
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 Alzheimer's disease model			

		50 mg/kg/day	Normal (not treated) male mice	CFCT	Gintonin enhanced memory by increasing pCREB and BDNF expression.	(Kim et al., 2016)
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., 2009)
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 cognitive impairment 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	*Codonopsis 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)
Luteolin	*Chrysanthemum morifolium*	10; 20 mg/kg/day	Streptozotocin (3 mg/kg/day) induced Alzheimer's disease 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-KB) 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., 2007)
Obtusifolin	*Cassia 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., 2009)
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 cognitive impairment by acting as a GABAA receptor antagonist.	(Kim et al., 2007)

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-KB 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	*Polygala tenuifolia*	3; 6; 12 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory deficit in male mice	MWM	Polygalacic acid reversed cognitive impairment 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-F11	*Panax quinquefolium*	1.6; 8 mg/kg/day	Aβ1-42 (410 pmol) induced Alzheimer's disease in male mice and not treated APP/PS1 mice	MWM, PAT	Pseudoginsenoside-F11 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 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	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-β), and regulating apoptotic proteins expression (increased Bcl2 and decreased Bax) in the hippocampus.	(Wang et al., 2016)
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	10; 50 mg/kg/day	Scopolamine (1 mg/kg/day) induced memory impairment	MWM	Sulforaphane improved memory and learning ability via cholinergic system modulation	(Lee et al., 2014)

	e.g., broccoli, cabbage, watercress, and Brussels sprouts		in female C57BL/6 mice		(increased ACh level and ChAT expression and decreased AChE activity) in the hippocampus and frontal cortex.	
Tanshinone I	*Salvia 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., 2007)
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	Aβ1-42 (300 pmol) induced Alzheimer's disease 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	OFT, EPM, MWM	Zerumbone reversed anxiety and depression-like behaviors and inhibited memory impairment. The mode of action is unknown but	(Jafarian et al., 2019)

			Sprague Dawley rats		might be related to the GABAA receptor.	
Z-Ligustilide	*Angelica gigas* / *Ligusticum 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)