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Pharmacotherapeutic potential of ginger and its compounds in age-related neurological disorders

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ABSTRACT

Age-related neurological disorders (ANDs), including neurodegenerative diseases, are multifactorial disorders with a risk that increases with aging. ANDs are generally characterized by common neuropathological conditions of the central nervous system, such as oxidative stress, neuroinflammation, and protein misfolding. Recently, efforts have been made to overcome ANDs because of the increase in age-dependent prevalence. Ginger, the rhizome of *Zingiber officinale* Roscoe, is a popular food spice and has a long history of use in traditional medicine for treating various disease symptoms. The structure-activity relationships of ginger phytochemicals show that ginger can be used to treat ANDs by targeting different ligand sites. This review shows that ginger and its constituents, such as 6-gingerol, 6-shogaol, 6-paradol, zingerone, and dehydrozingerone, are effective for ameliorating the neurological symptoms and pathological conditions of ANDs through by modulating cell death or cell survival signaling molecules. From this review, we conclude that the active ingredients in ginger have therapeutic potential in ANDs.

1. Introduction

Aging is a primary risk factor for many neurological disorders because brain tissue is more vulnerable to aging insults than other organs (Wyss-Coray, 2016). Age-related neurological disorders (ANDs) include neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD) and Parkinson's disease (PD), as well as other ANDs such as migraine and epilepsy (Jove, Portero-Otin, Naudi, Ferrer, & Pamplona, 2014; Mattson & Magnus, 2006). ANDs are characterized as multifactorial disorders that have common pathological features including neuronal loss, neuroinflammation, oxidative stress, and abnormal protein aggregation in the central nervous system (CNS) (Buendia et al., 2016; Jove et al., 2014; Mattson & Magnus, 2006). These disorders have been a large burden on public health due to an increase in the aging population, which is at high risk for onset of several diseases according to the Global Burden of Disease Study (Silberberg, Anand, Michels, & Kalaria, 2015; Thakur et al., 2016).

With no established cure, only a few drugs have been approved for the treatment but not prevention of ANDs (Bhullar & Rupasinghe, 2013). The existing AND drugs exert only symptomatic effects primarily by modulating neurotransmission (Berg, Belnoue, Song, & Simon, 2013). For example, three out of the five AD drugs are acetylcholinesterase (AChE) inhibitors, and the majority of PD drugs are levodopa or dopamine (DA) agonists (Anand, Gill, & Mahdi, 2014; Samudra, Patel, Womack, Khemani, & Chitnis, 2016). Despite enormous efforts and cost to identify a candidate drug that interacts with a single target with high specificity, or simultaneously regulates multiple targets via chimeric moieties for decades, there is still an unmet need for pharmacotherapeutic agents for ANDs (Bottegoni, Favia, Recanatini, & Cavalli, 2012; Dias & Viegas, 2014; Zheng,

Abbreviations: Aβ, amyloid beta; AβO, Aβ oligomer; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; AGEs, advanced glycation end products; AND, age-related neurological disorder; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CAT, catalase; COX-2, cyclooxygenase-2; CREB, cAMP response element-binding protein; d, day(s); DA, dopamine; EAE, experimental autoimmune encephalomyelitis; ERK, extracellular signal–regulated kinases; GPx, glutathione peroxidase; GSH, glutathione; h, hour(s); HO-1, heme oxygenase-1; H_2O_2, hydrogen peroxide; IL, interleukin; iNOS, inducible nitric oxide synthase; i.p., intraperitoneal; LPS, lipopolysaccharide; m, month (s); MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MDMA, 3,4-methylenedioxymethamphetamine; mir, micro-ribonucleic acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; N.D., not described; NF-κB, nuclear factor-κB; NGF, nerve growth factor; NO, nitric oxide; NPs, natural products; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PD, Parkinson's disease; PGE2, prostaglandin E2; p.o., oral administration; ROS, reactive oxygen species; RT, room temperature; SD, Sprague-Dawley; SN, substantia nigra; SOD, superoxide dismutase; ST, striatum; TNF-α, tumor necrosis factor-α; w, week(s); 6-OHDA, 6-hydroxydopamine

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Fridkin, & Youdim, 2014).

Natural products (NPs) include a variety of chemical compounds that have been evolutionarily selected for their ability to enhance the survival of an organism (Brahmachari, 2013). Due to diverse biological activities, they have widely been applied for human healthcare as a dietary supplement or traditional medicine for thousands of years (Ekor, 2014). Promising approaches for AND drugs may include identifying NPs that possess multiple pharmacological activities on different targets and validate them. Given that they contain a diversity of compounds in terms of structure and biological activity, NPs are likely to have a broader range of targets than synthetic compounds (Harvey, Edrada-Ebel, & Quinn, 2015; Koehn & Carter, 2005). In a systems-based approach, it was revealed that compounds derived from NPs are structurally more similar to human metabolites than conventional small-molecule drugs (Kim, Ryu, Lee, & Lee, 2015). This systematic approach may provide clues to the potentials of NPs for multi-target activities. Thus, NPs may be one of promising strategies for protecting and treating multifactorial diseases, such as ANDs, due to their multi-targeting actions with multiple components (Harvey et al., 2015; Koehn & Carter, 2005). Actually, the remarkable synergistic actions of ginger have been demonstrated. Orally fed ginger extract exhibited 2.4-fold higher anti-proliferative effects than an artificial mixture of ginger-derived compounds in human prostate tumor xenografts (Gundala et al., 2014). This result may be explained by the synergistic actions among active ginger compounds compared to the actions of each compound alone (Brahmbhatt, Gundala, Asif, Shamsi, & Aneja, 2013).

Recently, the evidence about the neuropharmacological effects of ginger has been accumulated. Here, after a brief overview of ginger, we reviewed the pharmacotherapeutic actions and the underlying mechanisms of ginger and its active compounds in ANDs and ANDs pathological conditions.

2. Ginger and its compounds

Ginger, the rhizome of *Zingiber officinale* Roscoe (Zingiberaceae family), is a widely used food ingredient and has been frequently prescribed for curing various symptoms, such as the common cold, nausea, asthma, cough, bleeding, and muscle pain in traditional medicine (Mascolo, Jain, Jain, & Capasso, 1989; Wang & Wang, 2005). Ginger has been also combined with other prescription drugs for brain diseases, such as paralysis by ischemic stroke and a nerve sedative (Xutian, Tai, & Yuan, 2014). Moreover, it has been applied to many diseases, such as cancer, emesis, bone disorders, metabolic dysfunction, and vascular disorders with clinical evidence (Fig. 1) (Azimi et al., 2016; Jiang et al., 2013; Lien et al., 2003; Lumb, 1994; Shidfar et al., 2015; Sohail, Chaudhry, Usman, Mian, & Ishaq, 2005). Approximately 400 types of constituents of ginger have been identified, including carbohydrates, lipids, terpenes, and phenolic compounds (Prasad & Tyagi, 2015; Tsuneki, Kimura, & Pancho, 2004). Chemically, isolated constituents from ginger are categorized into pungent and flavoring compounds. Pungent constituents from ginger include gingerols, shogaols, zingerones, gingerdiols, gingerdione, and capsaicin. The flavoring substances are categorized in two forms: volatiles and sesquiterpenes. Volatile constituents from ginger include zingiberene, pinene, camphene, cumene, borneol, bisabolene, and zingiberol whereas sesquithujene and zingiberol are belong to a sesquiterpenes class isolated from ginger (Brooks, 1916; Ekundayo, Laakso, & Hiltunen, 1988).

Pungent non-volatile compounds, such as gingerols, shogaols, zingerone and paradols are known to play a major role in various pharmacological actions of ginger (Jolad et al., 2004; Mashhadi et al., 2013; Prasad & Tyagi, 2015; Tsuneki et al., 2004). 6-Gingerol is the major pungent compound in fresh ginger with various biological properties and it has been connected to ameliorating or preventing chronic diseases in human and animal models (Wang, Zhang, Yang, & Yang, 2014a; Yusof & Anum, 2016). Its anti-aging effects has been reported, showing that it could inhibit vascular senescence by regulating the mammalian target of rapamycin pathway as an important modulator of aging processes (Shen, Jiang, Yang, Wang, & Zhu, 2016). 6-Shogaol, a dehydrated form of 6-gingerol, is another major pungent ingredient in dried ginger (Ok & Jeong, 2012). It is used as a marker compound for the quality control of ginger extracts, commercial products, and raw materials (Semwal, Semwal, Combrinck, & Viljoen, 2015). Recent studies have demonstrated that 6-shogaol is more stable due to the thermal liability of 6-gingerol by the presence of its β-hydroxyl keto group and has more potent pharmacological effects than 6-gingerol (Bhattarai, Tran, & Duke, 2001; Dugasani et al., 2010). 6-Paradol is produced from 6-shogaol by microbial metabolism and has been shown to possess antioxidative and anti-inflammatory activities similar to 6-shogaol (Chari, Manasa, Srinivas, & Sowbhagya, 2013; Jo et al., 2016). Zingerone is absent in fresh ginger but generated from gingerols by the reverse aldolization reaction when heating fresh ginger (Ahmad et al., 2015). The pharmacological actions of zingerone are varied, and they include antioxidant, anti-inflammatory, anti-cancer, anti-hyperlipidemic, and antibacterial activities (Hemalatha & Prince, 2015; Hsiang et al., 2013; Shin, Kim, Chung, & Jeong, 2005; Vinothkumar, Vinothkumar, Sudha, & Nalini, 2014). Zingerone also suppressed both oxidative stress and age-related inflammation via inhibition of the mitogen-activated protein kinase (MAPK)/nuclear factor-κB (NF-κB) pathway (Kim et al., 2010).

Interestingly, a computational investigation suggested ginger compounds have a multi-target binding ability with ligands while using a molecular docking system (Azam, Amer, Abulifa, & Elzwawi, 2014). The structure-activity relationship shows different sites of structures of

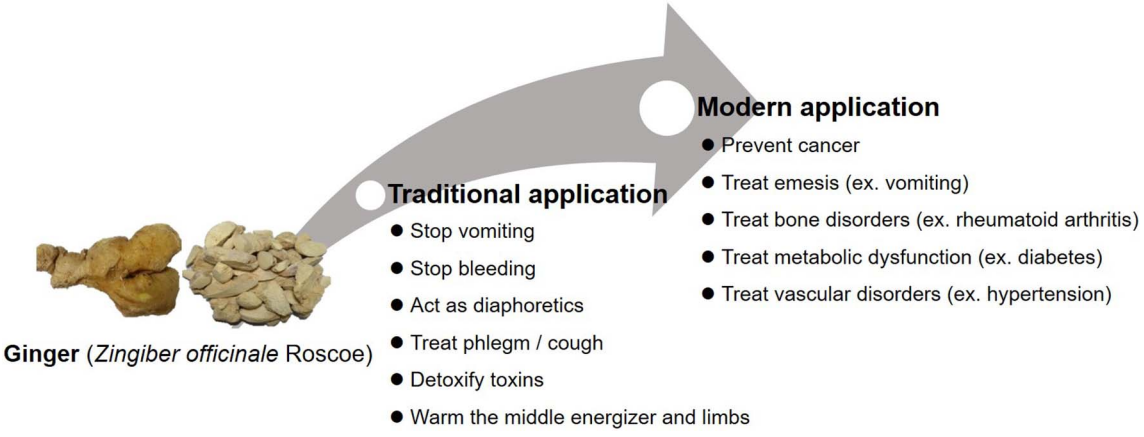

Fig. 1. Traditional and modern pharmacological applications of ginger. Ginger has been clinically used for various symptoms and diseases both in traditional and in modern medicine.

ginger compounds that display variable affinities to interact with all docked targets in a synergistic manner. In ginger compounds, p-OH, m-OCH_3, the linear chain between C_1 to C_5 exhibits a very important role and interact with different target sites of the ligand that ultimately exhibit different pharmacological activities (Azam et al., 2014). For example, in zingerone, replacement of an alkylated chain with a methyl group and the addition of C═O at the C_3 position showed significant antioxidant activity (Kabuto et al., 2005; Shin et al., 2005). In 6-shogoal, the presence of a double bond between the C_4 and C_5 position and the linear chain enhance the activity of this compound towards cyclooxygenase, AChE, and nitric oxide synthase as well as exhibits neuroprotective effects (Pan et al., 2008; Shim & Kwon, 2012; Tripathi, Maier, Bruch, & Kittur, 2007). In 6-gingerol, the addition of C═O at the C_3 position, an OH group at the C_5 position, and a replacement of a linear chain with an aromatic ring substituted with a hydrogen donor or acceptor group at the meta or para position reveal the dominant activity towards the inhibition of proinflammatory cytokines productions and cyclooxygenase-2 (COX-2) expression (Azam et al., 2014; Tripathi et al., 2007). Therefore, structure-activity relationships provide the potentials of ginger phytochemicals in ameliorating the ANDs by targeting different ligand sites. Actually, 6-gingerol, 6-shogaol, zingerone, and 6-paradol showed the pharmacological action and mechanisms in various ANDs from this review (Fig. 2).

3. Neuropharmacological actions of ginger in ANDs

Accumulated evidence shows that ginger and its compounds have neuropharmacological actions in ANDs, such as AD and dementia, PD, stroke, multiple sclerosis (MS), migraine, and epilepsy as well as ANDs pathological conditions (Tables 1, 2).

3.1. Effects of ginger and its compounds on AD and other dementia

AD, which is an irreversible and progressive neurological disorder, is the most common form of dementia and is a disease closely related to age, which indicates the global increased occurrence from approximately 5% of individuals over age 65 to 25% of those over age 85 (Reitz, Brayne, & Mayeux, 2011). More seriously, AD is rapidly becoming a major cause of human death, while other major causes, such as breast cancer, prostate cancer, heart disease, stroke, and acquired immune deficiency have decreased (Alzheimer's Association, 2015). The main pathological hallmark of an AD brain is abnormal aggregation of amyloid beta (Aβ) and tau proteins, which causes neuronal loss and synaptic damage (Iqbal, Liu, Gong, & Grundke-Iqbal, 2010; Murphy & LeVine, 2010). In addition, AD is accompanied by a decrease in cholinergic neurons and acetylcholine (ACh) levels in the basal forebrain, which are associated with short-term memory loss (Terry & Buccafusco, 2003). Delaying the cholinergic dysfunction is the mechanism of action for the current drugs for dementia, and they provide only symptomatic relief without a definite cure (Mufson, Counts, Perez, & Ginsberg, 2008). Furthermore, drug abuse, such as narcotics addiction, can induce cognitive deficits and show more prevalent among elderly people compared to young people (Dowling, Weiss, & Condon, 2008; Wang, Yao, Nie, & He, 2017). Ginger and its compounds ameliorated the memory and pathological changes induced by Aβ toxicity as well as other neurotoxicities such as scopolamine and narcotics.

3.1.1. Effects of ginger on Aβ neurotoxicity

Although the exact mechanism underlying AD pathogenesis is not fully understood, Aβ is regarded as a key pathogenic protein (Goldsworthy & Vallence, 2013). The neurotoxic properties of Aβ aggregates are mediated by multiple pathogenic factors, such as oxidative stress, neuroinflammation, mitochondrial breakdown, and synaptic dysfunction, which result in progressive memory and cognitive failure (Carrillo-Mora, Luna, & Laura, 2014). The earliest evidence of protective effects of ginger on Aβ neurotoxicity was provided by Grzanna et al. (Grzanna, Phan, Polotsky, Lindmark, & Frondoza, 2004). They found that treatment with ginger prevented the expression of pro-inflammatory cytokines and chemokines in human monocytic THP-1 cells exposed to $Aβ_{1–42}$ plaque insult. The effects of ginger in rats with AD induced by intracerebroventricular $Aβ_{1–40}$ plaque injection along with aluminum chloride ingestion was also observed (Zeng et al., 2013). Ginger treatment attenuated $Aβ_{1–40}$ plaque-induced behavioral dysfunction and neuronal cell death by lowering the inflammatory markers NF-κB and interleukin (IL)-1β as well as by increasing the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT). Surprisingly, the efficacy in this model was similar to huperzine A, which is a well-known anti-AD drug in China and a nutraceutical in the United States (Orhan, Orhan, & Gurkas, 2011).

Ginger-derived compounds showed consistent results of ginger extracts in Aβ-induced AD models. Pre-treatment with 6-gingerol protected neuronal cells from Aβ plaque-induced cytotoxicity in vitro. 6-Gingerol restored various $Aβ_{25–35}$ plaque-induced pathological alterations, including mitochondrial deoxyribonucleic acid (DNA) fragmentation, mitochondrial membrane potential, and apoptotic activity in SH-SY5Y cells (Lee, Park, Kim, & Jang, 2011). It modulated reactive oxygen species (ROS)-mediated oxidative stress by upregulating antioxidant factors such as glutathione (GSH), SOD, heme oxygenase-1 (HO-1), and nuclear factor erythroid-derived 2-like 2 (Nrf2) in $Aβ_{25–35}$ plaque-treated cells. 6-Gingerol treatment with PC12 cells suppressed the activation of serine/threonine kinase-glycogen synthase kinase 3β (GSK3β), which is directly linked to Aβ accumulation and synaptic damage in AD (Zeng et al., 2015). 6-Shogaol, which is an active compound of ginger, was explored for whether it contributes to the regulation of AD pathogenesis in APPswe/PSEN1dE9 double transgenic

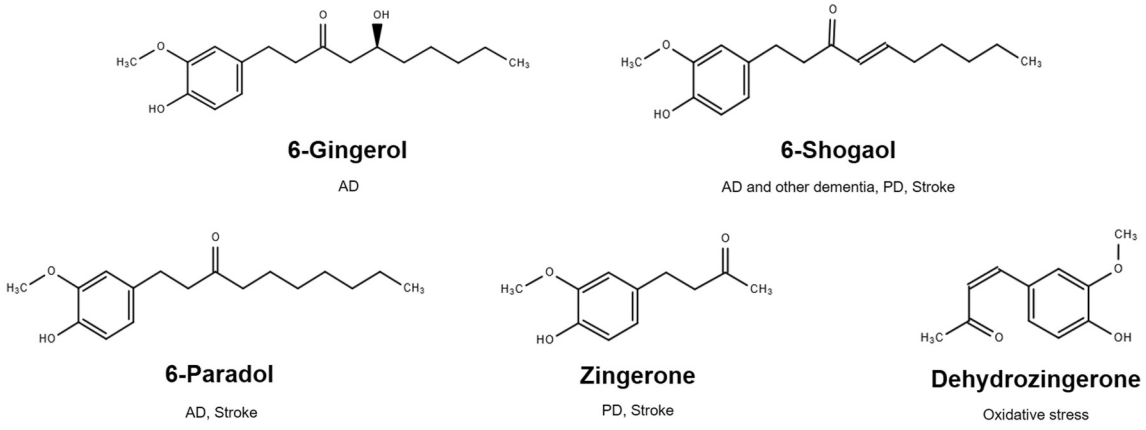

Fig. 2. Chemical structures of ginger-derived compounds with anti-ANDs activities. The matching ANDs are described below each compound name.

Table 1
Summary of studies on anti-ANDs effects of ginger extracts.

Category	Preparation methods	Subject	Insult	Sample treatment	Outcomes	References
AD	Provided by Ferrosan A/S, Soeborg, Denmark	Monocyte THP-1 cell	$A\beta_{1-42}$ plaque	10 μg/ml for 24 h	Inhibited the induction of pro-inflammatory cytokines (IL-1β, COX-2) and chemokines (macrophage inflammatory protein-1α, monocytechemoattractant protein-1, interferon gammainduced protein-10)	Grzanna et al., 2004
	Fermentation with *Aspergillus niger* Refluxed boiling (70% ethanol for 3 h at 80 °C)	Primary hippocampal cell	$A\beta_{1-42}$ plaque or $A\beta O_{1-42}$	25, 50 μg/ml for 18 h	Inhibited hippocampal cell death	Park et al., 2016
	N.D.	Female SD rats	$A\beta_{1-40}$ plaque + aluminum chloride	1, 2, 4 g/kg/d p.o. for 35 d	Attenuated memory deficits Increased expression of SOD and CAT Decreased expression of NF-κB and IL-1β	Zeng et al., 2013
Other dementia	Percolation (distilled water for 24 h at 37 °C)	–	–	–	Inhibited AChE activities Scavenged superoxide radical	Oboh et al., 2012
	Supercritical fluid extraction (Supercritical CO_2 for 6 h at 50 °C)	Male ICR mice	Scopolamine	5, 25, 125 mg/kg/d p.o. for 1 d	Ameliorated memory impairment	Lim et al., 2014
			–	5, 25, 125 mg/kg/d p.o. for 15 d	Enhanced memory function Elevated hippocampal NGF levels Increased expression of phosphorylated ERK and phosphorylated CREB Increased pre- and post-synaptic proteins	
	Percolation (80% ethanol for 24 h at RT	Male Wistar rats	Morphine –	50, 100, 200 mg/kg/d p.o. for 1 d	Ameliorated memory impairment Enhanced memory function	Gomar et al., 2014
	Percolation (70% ethanol for 24 h at RT)	Male SD rats	MDMA	100 mg/kg/d i.p. for 1 w	Attenuated memory deficits Inhibited hippocampal cell death Reversed Bcl-2 downregulation Reversed Bax upregulation	Mehdizadeh et al., 2012
	Provided by Thailand Institute of Scientific and Technological Research in Pathum Sthani, Thailand	Middle-aged women	–	400, 800 mg/d p.o. for 2 m	Enhanced working memory compared with placebo-treated group	Saenghong et al., 2012
PD	N.D.	Male C57BL/6 mice	MPTP	N.D.	Attenuated motor deficits Inhibited DA neuron death Increased striatal DA contents Inhibited microglial activation in both SN and GP Inhibited TNF-α, COX-2, NO, and iNOS in both SN and GP Upregulated the levels of mir-7 and mir-13	Ahmad et al., 2016
Stroke	Refluxed boiling (95% ethanol for 3 h)	Male Wistar rats	MCAO	100, 200, 300 mg/kg p.o. for 35 d	Improved memory dysfunction Inhibited hippocamapl cell death Reduced the brain infarct volume Increased the activity of SOD, CAT, and GPx	Wattanathorn et al., 2011
	Ginger pharmacopuncture (Distiled water for 15 min at 95 °C)			0.1 ml/kg Injection into Bai hui point	Ameliorated spatial memory Increased the activity of SOD, CAT, and GPx	Jittiwat & Wattanathorn, 2012
MS	Percolation (50% ethanol for 15 h at RT)	Female C57BL/6 mice	Myelin oligodendrocyte $glycoprotein_{35-55}$ peptidein Freund's adjuvant	200, 300 mg/kg/d i.p. for 27 d	Improved the EAE symptoms Modulated the mRMA expression of the IL-27 and IL-33 Decreased the levels of IL-17 and interferon gamma in serum	Jafarzadeh et al., 2014
Migraine	N.D.	Acute migraine patients (aged ≥ 18 years)	–	250 mg/d p.o. once	Decreased mean headaches severity Improved side effect profile than sumatriptan	Maghbooli et al., 2014
Epilepsy	Percolation (80% ethanol for 15 h at RT)	Male Swiss mice	PTZ	25, 50, 100 mg/kg/d i.p. for 2 d	Increased the seizure threshold	Hosseini & Mirazi, 2014

(continued on next page)

Table 1 *(continued)*

Category	Preparation methods	Subject	Insult	Sample treatment	Outcomes	References
	Benzene fraction of a petroleum ether extract	Male SD rats		5, 10, 20, 30 mg/kg i.p. for 1 d		Vishwakarma et al., 2002
Neuroinflammation, neuronal apoptosis, oxidative stress	Percolation (90% ethanol for 20 h at RT)	BV2 microglia cell	LPS	0.125, 0.25, 0.5 mg/kg for 20 h	Inhibited NO production Inhibited protein and mRNA expression of TNF-α, IL-1β, and IL-6 Inhibited NF-kB binding	Ho et al., 2013
	Hexane fraction (80% methanol for 14 h at 70 °C)			1, 10 μg/ml for 24 h	Inhibited NO, iNOS, and PGE2 induction Inhibited TNF-α and IL-1β expression Blocked MAPK and NF-κB activation	Jung et al., 2009
	N.D.	Male albino rats	Streptozotocin	500 mg/kg/d p.o. for 4, 6, 8 w	Reduced apoptosis and inflammation Modulated the astroglial response to the injury by reducing AChE expression	El-Akabawy & El-Kholy, 2014
	Grinded fresh juice	Male and female Wistar rats	Dichlorvos or lindane	100 mg/kg/d p.o. for 14 d	Decreased lipid peroxidation in brain Increased GSH, SOD, CAT, GPx, glutathione S- transferase, glutathione reductase and quinine reductase levels in brain	Sharma & Singh, 2012

Abbreviation:
N.D.; Not described, AD; Alzheimer's disease, MS; Multiple sclerosis, h; hour(s), d; day(s), w; week(s), m; month(s), RT; room temperature, AChE; acetylcholinesterase, MDMA; 3,4-methylenedioxymethamphetamine, i.p.; intraperitoneal, p.o.; oral administration, NGF; nerve growth factor, pERK; phosphorylated extracellular signal–regulated kinases, pCREB; phosphorylated cAMP response element binding protein, SOD; superoxide dismutase, CAT; catalase, GP; globus pallidus, GPx; glutathione peroxidase, GST; glutathione S-transferase, GR; glutathione reductase, QR; quinine reductase, NF-kB; nuclear factor-kB, IL; interleukin, COX-2; cyclooxygenase-2, MCP-1; monocyte chemoattractant protein-1, MIP-1α; macrophage inflammatory protein-1α, IP-10; interferon gamma-induced protein-10, NO; nitric oxide, EAE; experimental autoimmune encephalomyelitis, PTZ; pentylenetetrazole, MCAO; middle cerebral artery occlusion, SD; Sprague-Dawley, STZ; streptozotocin, PGE2; prostaglandin E2, MAPK; mitogen-activated protein kinase.

mice (Na, Song, Lee, Kim, & Kwon, 2016a). It led to reduced abnormal accumulated levels of Aβ, cysteinyl leukotriene receptor 1 (CysLT1R), and cathepsin B in the hippocampal and cerebral cortex regions as well as improved learning and memory impairment. Moon et al. provided evidence that ginger compounds have protective effects against the neurotoxicity induced by the Aβ oligomer (AβO), which is known to lead to the most cytotoxic form of Aβ (Haass & Selkoe, 2007; Sakono & Zako, 2010). They found that 6-shogaol attenuated $A\beta O_{1-42}$-induced memory loss, neuronal damage, and microglia activation in mice (Moon et al., 2014). In addition, two studies revealed that 6-paradol rich fermented ginger protected primary hippocampal neurons against neurotoxicity induced by $A\beta O_{1-42}$ or $A\beta_{1-42}$ plaque (Choi et al., 2017; Park, Choi, Park, Oh, & Ha, 2016). Taken together, ginger-derived compounds contributed to the anti-AD effects of ginger by attenuating Aβ plaque or AβO-induced memory dysfunction and neuronal cell death by regulating pathological alterations, including mitochondrial dysfunction, neuronal apoptosis, downregulation of anti-oxidant factors, and synaptic loss.

3.1.2. Effects of ginger on scopolamine-induced amnesia

Until now, therapeutic strategy for dementia has mainly focused on restoration of the cholinergic dysregulation leading to clinical symptoms (Godyń, Jończyk, Panek, & Malawska, 2016). It is known that the neurotransmitter ACh plays a key role in modulating memory ability and that antagonists of muscarinic ACh receptors, such as scopolamine, damage encoding processes of memory tasks without loss of previous consolidated memory information (Atri et al., 2004; Hasselmo & McGaughy, 2004). In this regard, several reports showed that ginger could modulate cholinergic signaling in the brain, which results in the recovery of scopolamine-induced memory dysfunction by inhibiting AChE activity (Lim et al., 2014; Oboh, Akinyemi, & Ademiluyi, 2012). In addition, a comparative analysis of computational binding interactions between the chemical structures of active ginger compounds and AChE revealed that ACh is the most promising target due to its lower binding energy (Azam et al., 2014). Thus, these results indicated the therapeutic potential of ginger in dementia as a modulator of ACh-dependent amnesia.

3.1.3. Effects of ginger on narcotics neurotoxicity

Several research studies on the pharmacological actions of ginger in narcotics-induced neurotoxicity have been reported. Because an aging brain adapts to changes less well, narcotics such as morphine and 3, 4-methylenedioxymethamphetamine (MDMA) could induce memory dysfunction in the elderly by disturbing memory formation and serotonin systems (Messing, Rigter, & Nickolson, 1982; Schilt et al., 2010). Treatment with ginger significantly reversed memory deficits induced by morphine, which impairs cognitive function by inhibiting cholinergic activity and memory retrieval ability in the hippocampus and ultimately disrupts working memory (Aguilar, Minarro, & Simon, 1998; Gomar, Hosseini, & Mirazi, 2014; Saha, Datta, & Sharma, 1991). MDMA, called ecstasy, also displayed rapid intracellular calcium influx, mitochondrial disruption, ROS production, and caspase-mediated apoptosis in hippocampal cells that contributes to memory deficits (Montgomery, Sitte, & McBean, 2010; Ros-Simo, Moscoso-Castro, Ruiz-Medina, Ros, & Valverde, 2013; Soleimani et al., 2012). Ginger alleviated MDMA-induced memory dysfunction and hippocampal damage by regulating expression of apoptotic proteins such as B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (Bax) (Mehdizadeh et al., 2012). These studies suggest that ginger can modulate memory impairment and pathological changes caused by narcotics neurotoxicity in elderly people.

3.1.4. Effects of ginger on memory enhancement

As the population ages, aging-induced cognitive decline is regarded as a prodromal stage of dementia that affects quality of life for older adults (Knopman & Petersen, 2014; Williams & Kemper, 2010). Then,

Table 2
Summary of studies on anti-ANDs effects of ginger-derived compounds.

Compound	Category	Subject	Insult	Sample treatment	Outcomes	References
6-gingerol	AD	SH-SY5Y or HT22 cell	$A\beta_{25-35}$ plaque	3, 10 μM for 24 h	Protected against $A\beta_{25-35}$-induced apoptotic cell death Inhibited disruption of mitochondrial membrane potential Inhibited Bax/Bcl-2 ratio Inhibited caspase-3 activation Inhibited intracellular ROS and reactive nitrogen species production Inhibited lipid peroxidation levels Increased GSH levels Increased HO-1 mRNA levels Increased Nrf2 phosphorylation	Lee et al., 2011
		PC12 cell	$A\beta_{1-42}$ plaque	80, 120, 200 μM for 48 h	Inhibited apoptotic cell death Inhibited intracellular NO and ROS production Increased SOD activity Increased glycogen synthase kinase 3 beta phosphorlyation	Zeng et al., 2015
6-shogaol	AD	Male ICR mice	$A\beta O_{1-42}$	10 mg/kg/d p.o. for 5 d	Ameliorated gliosis Alleviated memory impairment	Moon et al., 2014
		Male APPswe/PSEN1dE9 double transgenic mice	–	5, 20 mg/kg/d p.o. for 2 m	Reduced Aβ-induced cytotoxicity Ameliorated learning and memory impairment Inhibited cysteinyl leukotrienes receptor 1/cathepsin B expression	Na et al., 2016a
		HT22 cell	H_2O_2	10 μM for 3 h	Protected cholinergic neuronal hypofunction Increased choline acetyltransferase and choline transporter expression through a BDNF increase	Shim & Kwon, 2012
		Male ICR mice	–	5, 10, 20 mg/kg/d p.o. for 1 d	Enhanced memory function under normal condition Induced NGF levels and synaptogenesis	Moon et al., 2014
	PD	PC12 cell	6-OHDA	10, 20 μM for 24 h	Inhibited apoptotic cell death Inhibited caspase-3 activity Elevated GSH, HO-1, NAD(P)H dehydrogenase quinone 1, thioredoxin 1 and thioredoxin reductase 1 levels Stimulated Nrf2 translocation into nucleus	Peng et al., 2015
		Male C57BL/6 mice	MPTP	10 mg/kg/d p.o. for 3 d	Increased the number of tyrosine hydroxylase- positive neurons Suppressed TNF-α and NO levels Ameliorated motor dysfunction Inhibited reductions in tyrosine hydroxylase-positive cells in the SN and fibers in the ST Inhibited microglial activation Increased the levels of TNF-α, NO, iNOS, and COX-2 in both SN and ST	Park et al., 2013
	Stroke	Male C57BL/6 mice	MCAO	5, 20 mg/kg/d p.o. for 7 d	Attenuated behavioral deficits Reduced brain infarction Inhibited ROS production Inhibited TNF-α, IL-1β, COX-2, and iNOS Inhibited cysteinyl leukotrienes receptor 1 and MAPK signaling	Na et al., 2016b
			BCCAO	10 mg/kg/d p.o. for 3 d	Inhibited hippocampal cell death Inhibited caspase-3 activity in the hippocampus Inhibited microglial activation and TNF-α expression in the hippocampus	Ha et al., 2012
	Neuroinflammation, neuronal apoptosis, oxidative stress	Primary astrocytes	H_2O_2	10 μM for 24 h	Inhibited cell damage Decreased the expression of Bax and caspase-3 Increased the expression of Bcl-2 and Bcl-extra large Increased BDNF expression	Kim & Kwon, 2013
		Primary mixed cultures of astrocytes and microglia	LPS		Attenuated the cell death Reduced IL-1β, IL-6, iNOS and COX-2 expression Reduced NF-κB phosphorlyation	Shim et al., 2011

(continued on next page)

Table 2 *(continued)*

Compound	Category	Subject	Insult	Sample treatment	Outcomes	References
					Inhibited histone acetylation Increased heat shock protein 70 and heat shock factor protein 1 expression Attenuated the cell death Reduced Bax expression Increased Bcl-2 and BclxL expression Increased BDNF expression	Shim et al., 2012
		Primary mixed cultures of neurons and glia		1, 5, 10 μM for 24 h	Inhibited NO production Inhbited TNF-α, iNOS, COX-2 and PGE2 expression Inhibited NF-κB and MAPK activation Inhibited microglial activation	Ha et al., 2012
		Male C57BL/6 mice		5, 20 mg/kg/d p.o. for 3 d	Inhibited microglial activation in cortex and hippocampus	
Zingerone	PD	Male ICR mice	6-OHDA	6.5, 65 nM/kg/d i.p. for 1 d	Prevented reduction of striatal DA levels Increased striatal superoxide scavenging activity	Kabuto et al., 2005
				4 nmol/ml/d p.o. for 4 w	Enhanced 6-OHDA-induced reduction of striatal DA, 3,4-dihydroxyphenylacetic acid, and homovanillic acid levels Enhanced 6-OHDA-induced reduction of striatal CAT activity Increased striatal GPx activity	Kabuto & Yamanushi, 2011
		Male C57BL/6 mice	MPTP	10 mg/kg/d p.o. for 3 d	Inhibited reductions in TH-positive cells (in the SN) and fibers (in the ST) Inhibited microglial activation in both SN and ST Inhibited intracellular ROS production Increased the levels of phosphorylated ERK in SN Increased the levels of vesicular monoamine transporter 2 in SN	Choi et al., 2015
	Stroke	Male Wistar rats	MCAO	50, 100 mg/kg/d p.o. for 2 d	Decreased infarct volume and mitochondrial injury Improved behavioral outputs Decreased the caspase-3 and -9 activities Decreased the expressions of proapoptotic proteins (apoptotic protease activating factor-1 and Bax)	Vaibhav et al., 2013
6-paradol	AD	Primary hippocampal cell	$A\beta_{1-42}$ plaque or $A\beta O_{1-42}$	25, 50 μg/ml for 18 h	Inhibited hippocampal cell death	Choi et al., 2017
	Stroke	Male ICR mice	MCAO	1, 5, 10 mg/kg/d p.o. for 1 d	Reduced brain infarction Reduced neuroinflammation Ameliorated neurological deficit	Gaire et al., 2015
	Neuroinflammation, neuronal apoptosis, oxidative stress	BV2 microglia cell	LPS	1, 5, 10, 20 μg/ml for 24 h	Reduced NO production by inhibiting iNOS upregulation Decreased secretion of proinflammatory cytokines (IL-6 and TNF-α)	
Dehydrozingerone	Neuroinflammation, neuronal apoptosis, oxidative stress	Rat brain homogenate	–	–	Inhibited lipid peroxidation	Rajakumar & Rao, 1994

Abbreviation:
N.D.; Not described, AD; Alzheimer's disease, PD; Parkinson's disease, i.h.; Intrahippocampal injection, i.p.; intraperioneal injection, APP/PS1; Tg(APPswe,PSEN1dE9), ChAT; Choline acetyltransferase, ChTp; Choline transporter, BDNF; Brain-derived neurotrophic factor, NGF; Nerve growth factor, MPTP; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, LPS; Lipopolysaccharide, TH; Tyrosine hydroxylase, TNF-α; Tumor necrosis factor-α, NO; Nitric oxide, iNOS; Inducible nitric oxide synthase, COX-2; cyclooxygenase-2, SNpc; Substantia nigra pars compacta, ST; Striatum, ROS; Reactive oxygen species, RNS; Reactive nitrogen species, HIF-1α; Hypoxia-inducible factor-1α, 6-OHDA; 6-hydroxydopamine, DA; Dopamine, DOPAC; 3,4-Dihydroxyphenylacetic acid, HVA; Homovanillic acid, Apaf-1; Apoptotic protease activating factor-1, MCAO; Middle cerebral artery occlusion, 2VO; Bilateral common carotid arteries occlusion, VMAT2; Vesicular monoamine transporter 2, Nrf2; Nuclear factor (erythroid-derived 2)-like 2, HSP70; Heat-shock protein 70, HSF1; Heat shock factor protein 1, NQO1; NAD(P)H dehydrogenase quinone 1, Trx1; Thioredoxin 1, TrxR1; Thioredoxin reductase 1.

exploring interventions with enhancing memory function may be required to delay the progression of dementia. According to the clinical study by Saenghong et al., ginger enhanced memory function in conditions related to aging (Saenghong et al., 2012). They evaluated working memory and cognitive function of middle-aged women after oral administration of ginger extract, and the ginger treatment significantly improved scores for word recognition, digit vigilance, choice reaction, numeric working memory, and spatial working memory. Treating normal mice with ginger reinforced memory function by elevating hippocampal levels of nerve growth factor (NGF), which triggers the activation of extracellular signal–regulated kinases (ERK) and sequentially cAMP response element-binding protein (CREB) that lead to increases in synaptogenesis (Kim & Oh, 2013; Lim et al., 2014; Moon et al., 2014). These studies showed that ginger may improve cognitive decline in the early stage of dementia in advanced age.

Taken together, ginger showed anti-AD and anti-dementia effects by regulating Aβ plaque or AβO-induced memory dysfunction and neuronal cell death, ACh-dependent amnesia, narcotics-induced memory impairment and pathological changes by enhancing cognitive function. Ginger may be a good source for anti-AD therapeutics.

3.2. Effects of ginger and its compounds on PD

PD is another common AND with high prevalence that has shown a 5-fold increase in the population of PD patients from over the age of 60 to 85 (Reeve, Simcox, & Turnbull, 2014). The main pathological features of PD include progressive degeneration of DA neurons and cytoplasmic inclusions of Lewy bodies through misfolded α-synuclein accumulation in the midbrain (Samii, Nutt, & Ransom, 2004). With age, the accumulation of DNA defects and misfolded proteins accelerates the loss of DA neurons through an increase in toxic α-synuclein aggregation and mitochondrial dysfunction in the substantia nigra (SN) (Reeve et al., 2014). The DA neuronal loss in SN leads to striatal DA depletion, which results in severe motor deficits, such as resting tremor, rigidity, bradykinesia, and postural instability (Dauer & Przedborski, 2003; Lang & Lozano, 1998). The PD therapeutics of DA replacement therapy (levodopa and DA agonists) has not changed since 1970 (Pires et al., 2017). These drugs merely offer symptomatic relief and cannot delay disease. Because DA is auto-oxidative, a few years of levodopa treatment causes severe adverse effects, including motor fluctuations and levodopa-induced dyskinesia as well as DA neuronal damage (Muller, 2011).

The anti-PD actions of ginger and its compounds have been explored in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA)-induced PD models. Ahmad et al. showed that ginger extract significantly inhibited MPTP-induced motor impairment, DA neuronal damage, and striatal DA deletion (Ahmad, Amira, & Enas, 2016). Ginger showed anti-neuroinflammatory actions by inhibiting microglial activation and pro-inflammatory cytokine release. Ginger also upregulated the levels of micro-ribonucleic acid (mir)-153 and mir-7 which reduce ROS accumulation and protect cells against apoptosis in both SN and globus pallidus (GP) regions.

The anti-PD effects of two ginger compounds, 6-shogaol and zingerone, have been explored in PD models. 6-Shogaol inhibited MPTP-induced motor dysfunction and pathological changes, including DA neuron damage and gliosis accompanied by increased levels of inflammatory cytokines and chemokines (Park et al., 2013). 6-shogaol also reduced apoptotic cell death and ROS accumulation as well as upregulated nucleic translocation of Nrf2 against 6-OHDA neurotoxicity in PC12 cells (Peng et al., 2015). Zingerone induced ERK activation and vesicular monoamine transporter 2 expression, which led to the attenuation of MPTP-induced nigrostriatal damage (Choi, Bae, Park, & Jeong, 2015). Zingerone also controlled striatal DA metabolism and oxidative stress through restoration of anti-oxidant enzymes, such as CAT and glutathione peroxidase (GPx) and an increase in SOD scavenging actions in 6-OHDA-induced PD mice (Kabuto et al., 2005; Kabuto & Yamanushi, 2011).

Taken together, ginger and its compounds attenuate PD conditions induced by neurotoxins through regulating excessive oxidative stress and inflammatory events. It is meaningful that ginger may survive DA neurons as well as attenuate motor functions in PD.

3.3. Effects of ginger and its compounds on stroke

Both the incidence rates and poor outcomes of stroke increase with age, which indicates that over 80% of strokes occur in individuals > 65 years-old (Chen, Balami, Esiri, Chen, & Buchan, 2010). In elderly people, brain damage is more severe and endogenous production of antioxidant enzymes and neurotropic factors is absent after the onset of stroke (Arumugam et al., 2010). The severity of stroke outcomes in the aging brain is due to age-related loss of ovarian hormones and functional decline of the supporting cells of the brain, such as astrocytes and endothelial cells (Sohrabji, Bake, & Lewis, 2013).

Two independent studies have addressed the pharmacological potential of ginger and demonstrated the restorative effects of ginger in middle cerebral artery occlusion (MCAO)-induced memory loss and brain infarction (Jittiwat & Wattanathorn, 2012; Wattanathorn, Jittiwat, Tongun, Muchimapura, & Ingkaninan, 2011). MCAO is the most commonly used animal model for ischemic stroke and mimics the clinical scenario through blockade of the middle cerebral artery region (Kumar, Aakriti, & Gupta, 2016). Oxidative stress caused by ischemia and reperfusion after MCAO can induce neurodegeneration and production of antioxidant defense molecules (Chen et al., 2011). Both studies showed that the levels of antioxidant enzymes such as SOD, CAT, and GPx, increased in the hippocampus following treatment with ginger. Considering that clinical trials targeting pre-existing ROS using antioxidants have never provided desired results, it appears more promising to target ROS scavengers (Kleinschnitz et al., 2010). Thus, ginger may be a reliable source through which putative activators for the ROS scavenging enzymes SOD, CAT, and GPx can be isolated as new therapeutics for the aging brain.

Three ginger compounds were effective in stroke animal models. 6-Shogaol attenuated behavioral deficits and brain infarction induced by MCAO through downstream changes in oxidative stress, neuroinflammation, and MAPKs cell signaling via inhibition of CysLT1R (Na, Song, Lee, Kim, & Kwon, 2016b). Similar results were observed in another stroke model induced by bilateral common carotid arteries occlusion (BCCAO) following treatment with 6-shogaol (Ha et al., 2012). It attenuated hippocampal cell damage by inhibition of caspase-3 activity, microglial activation, and tumor necrosis factor-α production. Similarly, treatment with 6-paradol reduced neurological deficits, brain damage, and microglial activation after MCAO (Gaire et al., 2015). Zingerone also alleviated behavioral and histological defects by reducing brain ischemic damage with alterations in oxidative stress and apoptotic markers in the cortex and hippocampus in MCAO rats, respectively (Vaibhav et al., 2013). This action may have originated from the structural similarity to curcumin because vanillyl ketones attenuated vascular atherosclerosis in the age-related decline of endothelial functions (Profumo et al., 2016; Yogosawa et al., 2012).

These results support the fact ginger possesses therapeutic potential in stroke, due to its efficacy at reducing oxidative stress, neuroinflammation, and apoptosis. This result implies that ginger and its active components may control stroke-induced behavioral deficits and brain damage.

3.4. Effects of ginger on MS

Age affects the brain lesions of MS through the decrease of myelinating oligodendrocytes, which results in motor disability in MS patients (Manouchehrinia et al., 2017; Rist & Franklin, 2008; Ruckh et al., 2012; Tortorella et al., 2005). MS, which is an inflammatory and autoimmune neurological disorder, is characterized by a cascade of

pathological events, such as demyelination and axonal degeneration through autoimmune activation, that lead to overproduction of pro-inflammatory cytokines (Ciccarelli et al., 2014; Gold & Wolinsky, 2011; Hemmer, Archelos, & Hartung, 2002). Ginger has been shown to ameliorate these MS lesions according to the report by Jafarzadeh and his colleagues. In this study, it was revealed that ginger significantly regulated MS symptoms and levels of inflammatory cytokines, including IL-27 and IL-33, in experimental autoimmune encephalomyelitis (EAE) mice (Jafarzadeh et al., 2014). IL-33 activates innate immune cells through induction of Th1- and Th2-type responses, while IL-27 suppresses Th17-type hypersensitivity by inhibiting the production of IL-17 in EAE conditions, which reproduces the key clinical and pathological features of MS (Constantinescu, Farooqi, O'Brien, & Gran, 2011; Diveu et al., 2009; Smithgall et al., 2008). However, there is a concern that these results may not represent the pharmacological effects of ginger on the human MS brain because it is unclear whether the ginger affects neuron demyelination. To support the hypothesis, further investigation of the demyelination model using Theiler's murine encephalitis virus or cuprizone will be needed (McCarthy, Richards, & Miller, 2012; Torkildsen, Brunborg, Myhr, & Bo, 2008).

In short, ginger significantly alleviated EAE symptoms through the modulatory function of innate immune responses, and these actions may contribute to the therapeutic potential of ginger for the treatment of MS.

3.5. Effects of ginger on migraine

Migraine, which is the most common form of headache accompanied by a focal neurological disturbance with visual and motor symptoms, is closely linked to age-induced change in brain structures, such as cortical thinning (Burstein, Noseda, & Borsook, 2015; Chong, Dodick, Schlaggar, & Schwedt, 2014). Despite continuous developments in the field of migraine treatment, which has provided further opportunities to select more specific and effective remedies, many patients prefer to relieve headaches through complementary and alternative medicine instead of chemical drugs with adverse events, including gastrointestinal symptoms and anorexia (D'Andrea, Cevoli, & Cologno, 2014; Diener, 2013; Whyte & Tepper, 2009). In this situation, a double-blind randomized controlled clinical study revealed that ginger is highly effective for treating acute migraine patients without pre-symptoms (Maghbooli, Golipour, Moghimi Esfandabadi, & Yousefi, 2014). Both sumatriptan as a conventional drug and ginger capsules reduce the pain and severity of migraine attacks within 2 h of ingestion. However, subjects treated with ginger had fewer side effects compared to the sumatriptan-treated group. This result is consistent with previous studies on Gelstat®, which is a sublingual over-the-counter combination drug comprised of ginger and feverfew, which is the plant *Tanacetum parthenium* L. that is traditionally used the treatment of migraine (Cady et al., 2011; Cady, Schreiber, Beach, & Hart, 2005). In addition, the anti-emetic effects of ginger may reduce nausea symptoms caused by acute migraine (Viljoen, Visser, Koen, & Musekiwa, 2014). Consequently, these results indicate that ginger may effectively ameliorate migraine symptoms without adverse effects compared to conventional drugs.

3.6. Effects of ginger on epilepsy

It has been reported that ginger showed remarkable actions on epilepsy clinically characterized by recurrent seizures. Epilepsy in elderly people specifically has fewer pre-symptoms and longer duration of postictal confusion compared to younger patients (Cloyd et al., 2006; Ferlazzo, Sueri, Gasparini, & Aguglia, 2016; Ramsay, Rowan, & Pryor, 2004). This effect may be associated with the extensive changes in brain structure that occur due to accelerating ventricular expansion with increasing age (Dabbs et al., 2012). Ginger extract was effective for reducing the duration and incidence of seizures induced by pentylenetetrazole (PTZ), which is a well-known inducer of epilepsy-like symptoms in an age-dependent manner (Fanelli & McNamara, 1986; Kondziella, Bidar, Urfjell, Sletvold, & Sonnewald, 2002; Vishwakarma, Pal, Kasture, & Kasture, 2002). More recently, another study also showed similar results after treatment with ginger extract in mice (Hosseini & Mirazi, 2014). Both studies demonstrated that ginger treatment significantly prevented myoclonic and clonic seizures as well as forelimb tonic extension. These actions of ginger may be derived from the inhibitory activities of 6-gingerol on the production of nitric oxide (NO), which activates the soluble guanylyl cyclase that regulates the seizure threshold (Ippoushi, Azuma, Ito, Horie, & Higashio, 2003; Nidhi, Balakrishnan, & Pandhi, 1999). In addition, it is possible that 6-gingerol and zingerone, as an agonist of vanilloid receptors, modulate seizure activity and may contribute to the anticonvulsant activities of ginger (Calixto, Kassuya, Andre, & Ferreira, 2005; Gonzalez-Reyes, Ladas, Chiang, & Durand, 2013). Taken together, ginger and its compounds inhibited epileptic symptoms, such as recurrent seizures and involuntary movement, and these findings have provided strong evidence for the potential use of ginger as an anti-epileptic treatment.

3.7. Effects of ginger and its compounds on pathological conditions of ANDs

Ginger has been explored for its efficacy in neuropathological features that are commonly observed in ANDs, including oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, and apoptotic cell death, which could directly lead to the onset and progression of disease (Deleidi, Jaggle, & Rubino, 2015; Ward, Zucca, Duyn, Crichton, & Zecca, 2014; Wyss-Coray, 2016). Increased oxidative stress and neuroinflammation due to aging of the brain stimulate mitochondrial dysfunction and apoptotic injury in CNS neurons (Aktas, Ullrich, Infante-Duarte, Nitsch, & Zipp, 2007; Loh, Huang, De Silva, Tan, & Zhu, 2006). There are two lines of evidence indicating that ginger extract has an anti-neuroinflammatory effect on ANDs-related pathological conditions. Treatment with ginger extract downregulated the expression of pro-inflammatory cytokines and NF-κB in BV2 microglia stimulated with lipopolysaccharide (LPS) (Ho, Chang, & Lin, 2013; Jung, Yoon, Park, Han, & Park, 2009). Ginger extract has been reported to exhibit a neuroprotective effect against streptozotocin-induced diabetic encephalopathy accompanied by oxidative stress and gliosis in rats (El-Akabawy & El-Kholy, 2014). This insult mimics the pathology of AD, such as hippocampal atrophy, Aβ aggregation, and synaptic loss (Wang, Yin, et al., 2014). Ginger also inhibited oxidative stress induced by pesticides such as dichlorvos and lindane through an increase in endogenous anti-oxidant enzymes, including SOD, CAT, and GPx (Sharma & Singh, 2012).

6-Shogaol showed potent neuroprotective actions against hydrogen peroxide (H_2O_2) or LPS insult in primary glial cells (Ha et al., 2012; Kim & Kwon, 2013; Shim, Kim, Choi, Kwon, & Kwon, 2011; Shim, Kim, Kwon, & Kwon, 2012). Its neuroprotective actions were dependent on inhibiting expression of pro-inflammatory cytokines and pro-apoptotic proteins and increasing expression of heat shock proteins, anti-apoptotic proteins, and growth factors. 6-shogaol also restored H_2O_2-induced downregulation of the two cholinergic markers acetyltransferase and choline transporter in HT22 cells (Shim & Kwon, 2012). Interestingly, this effect was blocked by deactivating the brain-derived neurotropic factor (BDNF) signaling pathway. 6-Paradol showed the inhibitory effect of NO production and secretion of pro-inflammatory cytokines in LPS-activated BV2 microglia, which leads to neuroprotective actions against stroke-induced brain damage (Gaire et al., 2015). Taken together, ginger has the potential to regulate ANDs-related pathological conditions and to be a supplementary therapeutic for ANDs.

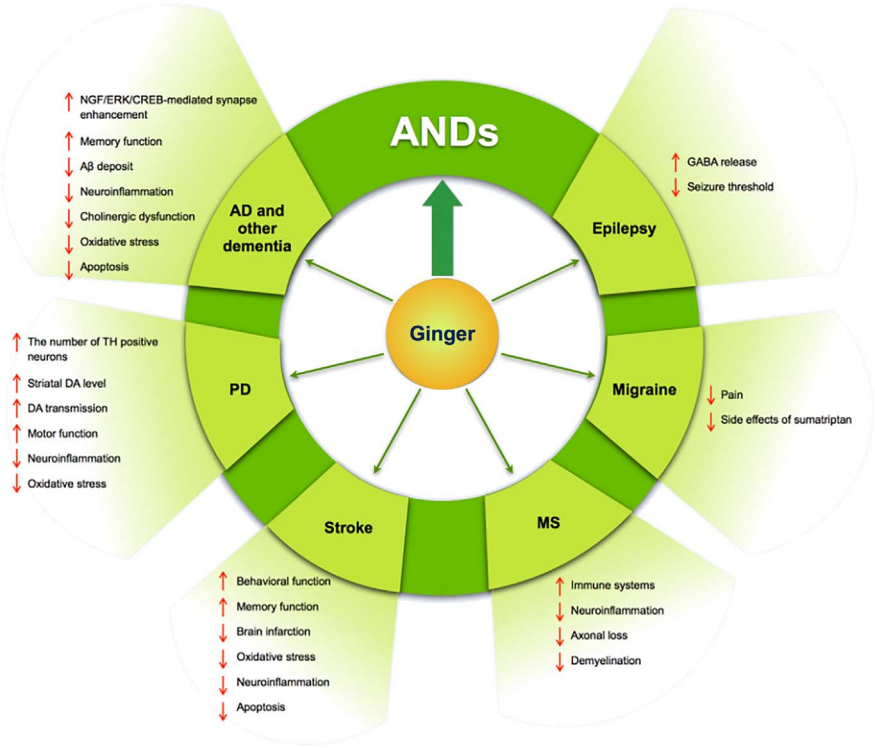

Fig. 3. Neuropharmacological effects of ginger and its compounds on ANDs. Ginger affects AD and other dementia, PD, stroke, MS, migraine, and epilepsy via each underlying mechanism. Down-arrow (↓) and up-arrow (↑) signs indicate inhibition and activation by ginger treatment, respectively. GABA, γ-aminobutyric acid; TH, tyrosine hydroxylase.

4. Summary and perspectives

In this review, we discussed the current evidence for the pharmacological potential of ginger and its compounds in the treatment of ANDs (Fig. 3). Ginger has been validated for its therapeutic efficacy not only in AND models but also in ANDs-related pathological conditions. It ameliorates disease-specific symptoms and pathological changes by controlling the pathogenesis of ANDs. Furthermore, ginger-derived active compounds, including 6-gingerol, 6-shogaol, zingerone, dehydrozingerone, and 6-paradol, exhibited various anti-AND effects in preclinical studies that demonstrated neuropharmacological actions along with each mode of action. In particular, 6-shogaol remarkably shows the multiple neuropharmacological actions on ANDs compared to other ginger-derived compounds (Fig. 4). These features of 6-shogaol may be involved in the strong binding affinity to human serum albumin, which is a major transport protein in blood circulation and could affect the pharmacodynamic effectiveness (Feroz, Mohamad, Lee, Malek, & Tayyab, 2015).

ANDs remains a challenge to treat because the exact etiology has not yet been identified. Moreover, their pathogenesis represents a complex network that involves multiple signaling pathways but no feedback system to adjust imbalance after the onset of disease. Numerous investigations are being conducted on the effects of NPs in brain disease pathology, such as inflammation, oxidative stress, mitochondria dysfunction, and protein misfolding. Notably, ginger and its constituents ameliorated multiple pathological conditions of brain degeneration in various in vitro and in vivo models through their antioxidant, anti-inflammatory, and protein-modifying properties. As a multi-target agent, ginger may be a promising therapeutic candidate for the treatment of ANDs and brain aging. Additionally, its main constituents, such as 6-gingerol and 6-shogaol, have also been validated to contribute to the pharmacological efficacy of ginger. Thus, the standardization of ginger samples and constituents by high performance liquid chromatography and gas chromatography fingerprinting will provide valuable insight into the use of ginger as a potent natural medicine.

Although ginger and its compounds may have strong potential for the treatment of ANDs, studies on their safety and pharmacodynamics and pharmacokinetics will offer a better understanding of these compounds for developing a clinically available drug from ginger. Until now, no significant side effect, except platelet aggregation, has been reported from preclinical studies on the anti-tumorigenic, anti-hyperlipidemic, and anti-emetic effects of ginger (Marx et al., 2015). There is no evidence that ginger affects the pharmacodynamic interactions between prescribed drugs, such as warfarin and nifedipine. According to the pharmacokinetic analysis of the major constituents, including 6-gingerol, ginger compounds appear to have a short half-life and low toxicity in humans (Qiu et al., 2015). More studies are needed to check the toxicity or side effects of long-term or large-dose administration and to determine potential in vivo interactions between ginger compounds and other molecules that play a key role in regulating gene expression and the action of human cytochrome P450. Structural conformation by heating and dehydration as well as enzyme reactions that catalyze chemical modifications may affect the biological activity of ginger-derived metabolites. Future studies are required to delineate the relationship between the structure and pharmacological efficacy of ginger compounds in AND models, including the major constituents, such as 6-gingerol and 6-shogaol, as well as minor constituents. The ultimate goal of such efforts will be to identify a potential candidate from ginger that has the most potent pharmacological efficacy with the least deleterious drug interactions in AND models.

It is possible that ginger and its compounds may function actively under non-pathological or pre-disease conditions, such as chronological aging. The identification of new biomarkers for brain aging and their targets, whose specific interactions trigger or accelerate the progression of brain aging and neurodegeneration, will be a critical step for expanding the applications of ginger as a new agent against ANDs. For example, various metabolic pathways may contribute to the pathogenic transition from a normal to a disease state, such as by increasing glucotoxicity through gluco-oxidation (Houtkooper et al., 2011; Kawahito, Kitahata, & Oshita, 2009). In this regard, it will be worth examining whether ginger and its compounds have regulatory effects in glucotoxicity-induced ANDs by inhibiting the formation of advanced glycation end products (AGEs), which reduces the toxicity of AGEs, and

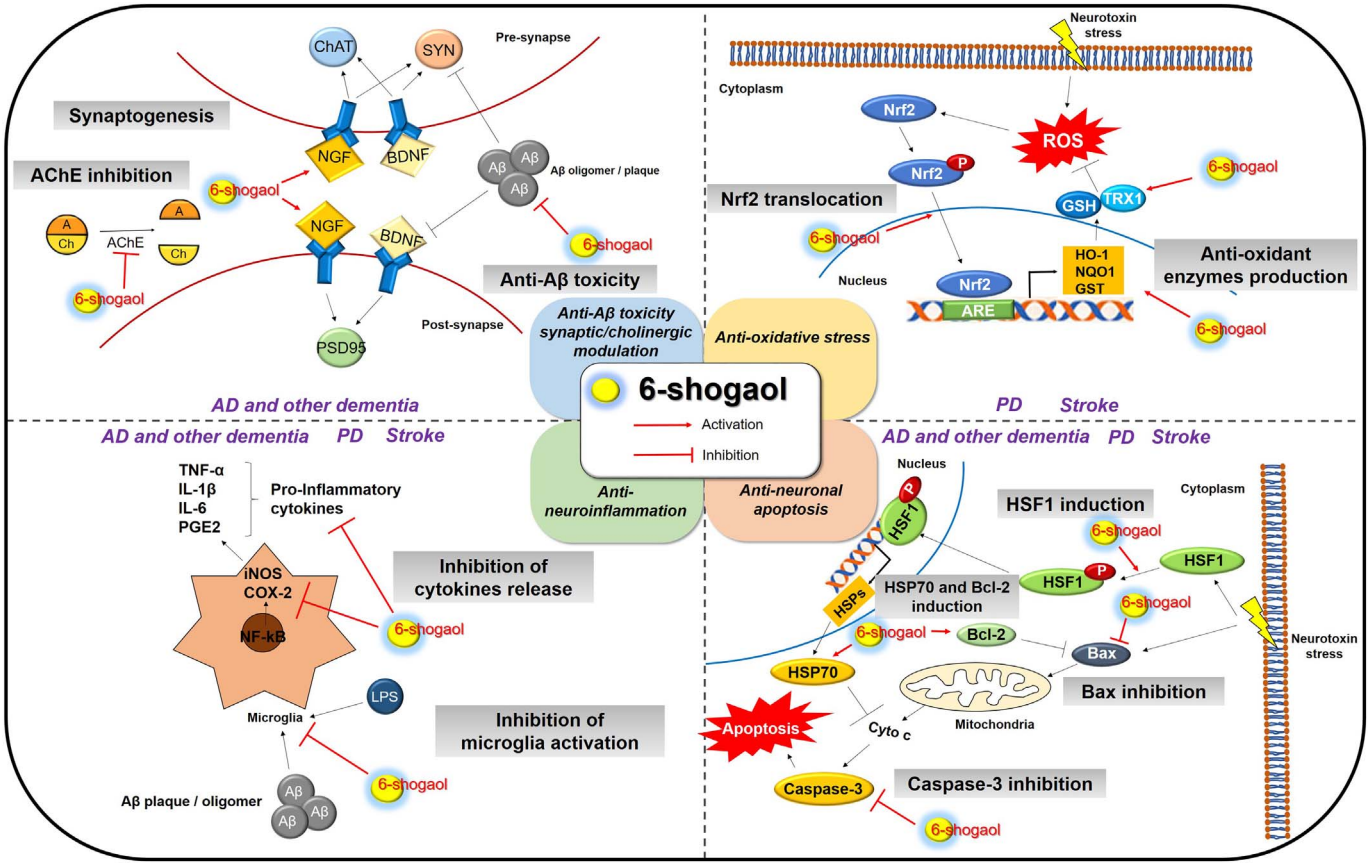

Fig. 4. 6-Shogaol as a multi-acting ginger-derived compound for ANDs. 6-Shogaol shows the various neuropharmacological activities via anti-Aβ toxicity, modulation of synaptic and cholinergic functions, anti-oxidative stress, anti-neuroinflammation, and anti-neuronal apoptosis. The red lines (—|) and arrows (→) mean the inhibitory and stimulating actions of 6-shogaol, respectively. The black ones mean inhibition and activation for related molecules, respectively. A, acetate; ARE, antioxidant responsive element; Ch, choline; ChAT, choline acetyltransferase; Cyto c, cytochrome *c*; GST, GSH S-transferase; HSF1, heat shock factor protein 1; HSP, heat shock proteins; NQO1, NAD(P)H dehydrogenase quinone 1; p, phosphorylated; PSD95, postsynaptic density protein 95; SYN; synaptophysin; TRX1; thioredoxin 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

promotes the removal of AGEs.

From this review, we have a better understanding of the potential of ginger to be used as a pharmacotherapeutic agent for managing NDDs and other ANDs in addition to its long-term use as a safe food ingredient and herbal medicine. We expect that future studies will identify an innovative drug candidate from ginger for the treatment of ANDs, whose prevalence is gradually increasing in modern society due to the aging population.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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