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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

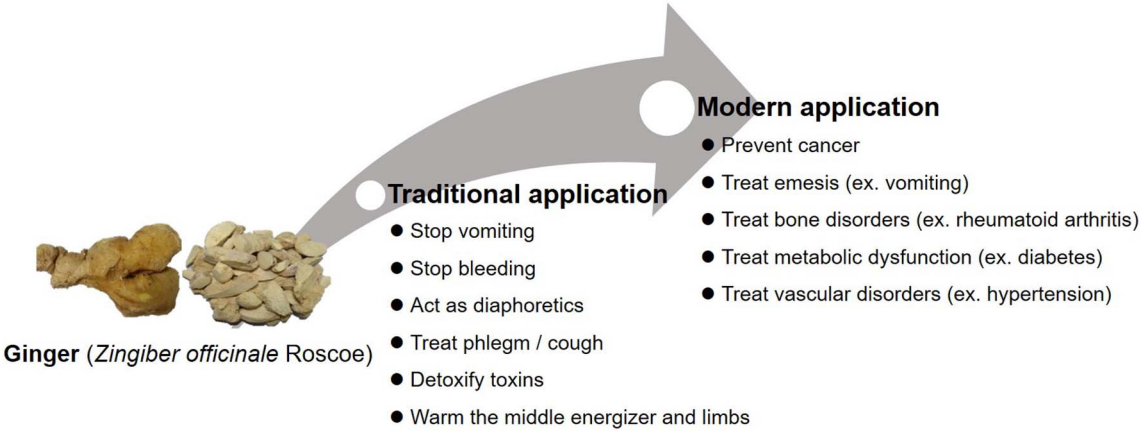

Fig. 1. Traditional and modern pharmacological applications of ginger. Ginger has been clinically used for various symptoms and diseases both in traditional and in modern medicine.