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REVIEW PAPER

Phytochemicals in Ischemic Stroke

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Abstract Stroke is the second foremost cause of mortality worldwide and a major cause of long-term disability. Due to changes in lifestyle and an aging population, the incidence of stroke continues to increase and stroke mortality predicted to exceed 12 % by the year 2030. However, the development of pharmacological treatments for stroke has failed to progress much in over 20 years since the introduction of the thrombolytic drug, recombinant tissue plasminogen activator. These alarming circumstances caused many research groups to search for alternative treatments in the form of neuroprotectants. Here, we consider the potential use of phytochemicals in the treatment of stroke. Their historical use in traditional medicine and their excellent safety profile make phytochemicals attractive for the development of therapeutics in human diseases. Emerging findings suggest that some phytochemicals have the ability to target multiple pathophysiological processes involved in stroke including oxidative stress, inflammation and apoptotic cell death. Furthermore, epidemiological studies suggest that the consumption of plant sources rich in phytochemicals may reduce stroke risk, and so reinforce the possibility of developing preventative or neuroprotectant therapies for stroke. In this review, we describe results of preclinical studies that demonstrate beneficial effects of phytochemicals in experimental models relevant to stroke pathogenesis, and we consider their possible mechanisms of action.

Keywords Stroke · Inflammation · Neuronal cell death · Ischemia · Natural products · Phytochemical

Introduction

The World Health Organization (WHO) has reported that stroke is the second leading cause of mortality worldwide and responsible for over six million deaths each year (The top 10 causes of death 2014). Stroke is also a leading cause of permanent disability and is recognized as a major economic health burden in developed countries. Numerous lifestyle risk factors such as obesity, diabetes mellitus, hypertension, hyperlipidemia, cigarette smoking, physical inactivity and excessive consumption of alcohol have all been associated with increasing the likelihood of stroke (Goldstein et al. 2011).

Aging, a non-modifiable risk factor, increases the incidence of stroke. It is predicted from statistical models that the incidence of stroke will increase from 1.6 to 2.7 per 1000 people to 14.3 per 1000 people over 45 years of age, and approximately 120 per 1000 people over 75 years of age (Mukherjee and Patil 2011; Strong et al. 2007). The

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emergence of an aging population in developed countries will inevitably increase the incidence of stroke annually where it is predicted that worldwide mortality from stroke will be over 12 % by the year 2030 (Mukherjee and Patil 2011; Strong et al. 2007). These alarming statistics reinforce the notion that stroke is indeed a major public health concern with enormous financial implications to the healthcare system worldwide. Hence, the need for comprehensive research in the field of stroke is warranted to advance understanding of stroke pathophysiology and to explore newer ways to treat stroke patients.

Currently, there are two major therapeutic strategies for ischemic stroke—arterial recanalization and neuroprotection. In clinical practice, arterial recanalization is the surgical removal of a blood clot by intracranial clot aspiration and stent retriever devices (Penumbra system and Solitaire and Trevo devices), or by pharmacological thrombolysis using recombinant tissue plasminogen activator (r-tPA) (NINDS 1995; Smith et al. 2008; Taschner et al. 2011). Intravenous r-tPA (Alteplase) is the only pharmacological treatment for acute ischemic stroke, which is approved by the US Food and Drug Administration (FDA) (NINDS 1995). However, the use of r-tPA for the treatment of ischemic stroke in the acute phase has major limitations, including a narrow therapeutic window of 3–4.5 h, an elevated incidence rate of intracranial hemorrhage, neuronal excitotoxicity, and inadequate capacity to rescue dying neurons (Hacke et al. 2008; Kelly et al. 2006; Nicole et al. 2001; Ning et al. 2006).

Another paradigm for treating acute ischemic stroke is neuroprotection. The notion that the ischemic cascade can be interfered, and neurons in the ischemic penumbra salvaged from irreparable damage by pharmaceutical agents gave rise to the development of using neuroprotective agents in ischemic stroke. During the past decade, several agents with neuroprotective functions have undergone clinical trials by targeting a single molecular pathway using a Na^+ channel blocker (e.g., Fosphenytoin), a Ca^{2+} channel blocker (e.g., Nimodipine), *N*-methyl-D-aspartic acid (NMDA) glutamate receptor antagonists (e.g., Selfotel), free radical scavengers (e.g., Trilizad, NX-059) and anti-inflammatory therapies (e.g., Enlimomab) (Ahmed et al. 2000; Chan et al. 1998; Davis et al. 2000; Furuya et al. 2001; van der Worp et al. 2002). Despite evidence that brain cell death, neurological deficit and infarct size in animal stroke models can be decreased by neuroprotective agents, each of these pharmacological agents had failed in human clinical trials (Cheng et al. 2004; Green 2002). The discrepancies between such therapeutic results in animal stroke studies and human clinical trials boil down to several factors such as species differentiation, the use of stroke models to mirror advanced age and confounding diseases such as diabetes mellitus and hypertension that are more commonly observed in clinical practice (Howells et al. 2010; O'Collins et al. 2011; Schaller 2007; Wang et al. 2003). In consideration of such differences between animal stroke models and human patients, it leaves the possibility that the combination of therapeutic approaches on human patients may provide beneficial effects through the regulation of multiple pathways involved in stroke.

Over the last few decades, many researchers have revealed that chemicals extracted from different organisms such as bacteria, sponges, lichens, fungi, and animals can modify the disease outcome by targeting pathophysiological mechanisms involved in human diseases (Lordan et al. 2011; Salvador-Reyes and Luesch 2015; Teixeira et al. 2014; Huang et al. 2013; Smith and Clinard 2014; Zhang et al. 2013a, b). Moreover, in the category of plants, it has been shown that common vegetables and fruits contain numerous biologically active components and that regular consumption of vegetables and fruits leads to enhanced health outcomes, such as reduction of cardiovascular diseases and stroke risk (Joshipura et al. 2001). Many experimental studies have shown that treatment with natural products, such as dietary polyphenols, can improve injury outcome in animal models of ischemic stroke (de Gaetano et al. 2002; Moosavi et al. 2016). In addition, epidemiological evidence indicates that natural products can be beneficial in treating human stroke (Larsson et al. 2013). There have been a number of controlled trials that evaluated the efficacy and safety of natural products in the treatment of human ischemic stroke (Chen et al. 2013a, b; Oskouei et al. 2013; He et al. 2011; Poppitt et al. 2009; Jung et al. 2003). These studies showed that natural products targeting various mechanisms involved in stroke pathogenesis could potentially attenuate and, partially or fully, reverse the neurological impairments in stroke patients. However, the preclinical and epidemiologic data to support the use of natural products in human stroke has not been successfully translated to clinical practice.

This article reviews our current understanding of neuroprotective actions of phytochemicals with regard to stroke pathogenesis and explores their potential applications in clinical practice.

Pathophysiology of Stroke

Stroke is categorized into two major subtypes, ischemic and hemorrhagic stroke. Approximately, 80–85 % of all stroke cases are ischemic stroke and are triggered by formation of a blood clot within a cerebral artery. For hemorrhagic stroke, which is initiated by the rupture of a cerebral blood vessel, it accounts for roughly 15–20 % of all strokes (Amarenco et al. 2009; Gilgun-Sherki et al. 2002). Ischemic stroke occurs when cerebral blood flow is

attenuated briefly or lastingly and is characterized by the formation of two distinct affected regions of brain tissue, a central ischemic core and a surrounding ischemic penumbra or peri-infarct zone that receives some collateral blood supply (Kumar et al. 2010; Lo 2008). In the ischemic core region, brain cells undergo necrotic cell death producing an area that is electrically, metabolically and functionally inactive (Mehta et al. 2007). However, neurons in the ischemic penumbra, which normally appears among the normal healthy tissue and ischemic core, are metabolically active, but electrically and functionally compromised (Astrup et al. 1981; Hossmann 1994; Moskowitz et al. 2010).

The pathological mechanisms of ischemic brain injury are highly dependent on a number of factors including the severity and duration of ischemia. Although recanalization of the occluded artery is the principal objective of acute reperfusion treatment, restoration of blood flow may, paradoxically, be detrimental and trigger reperfusion injury, potentially further propagating the extent of ischemic injury and derailing efforts at recovery (Brouns and De Deyn 2009; Suwanwela and Koroshetz 2007). In general, the ischemic cascade and reperfusion injury are characterized by the following biochemical events—bioenergetic failure, ionic imbalance, acidosis, excitotoxicity, oxidative stress and inflammation, culminating in cell death via necrosis or apoptosis (Fig. 1).

Depolarization and Excitotoxicity in the Early Phase of Stroke

The initial insult triggered by cerebral ischemia is bioenergetic failure due to oxygen and glucose deprivation and, consequently, reduced adenosine triphosphate (ATP) production in the mitochondria (Hertz 2008; Hertz and Dienel 2002; Hertz et al. 2007; Rossi et al. 2007). The deficiency of ATP results in ATP-dependent ion pump dysfunction including the plasma membrane Na^+/K^+-ATPase and Ca^{2+}-ATPase, which elicits rapid deterioration of ionic gradients across the plasma membrane, resulting in excessive influx of Ca^{2+} and Na^+ ions, and efflux of K^+ ions (Kaplan 2002; Khanna et al. 2014; Lipton 1999; Mongin 2007; Song and Yu 2014). The increased levels of Na^+ ions in neurons and glial cells can cause an osmotic movement of water through aquaporins into the cell, leading to cytotoxic swelling (Khanna et al. 2014; Song and Yu 2014). Anaerobic glycolysis leads to an increased production of hydrogen ions (H^+) in the surrounding environment, another early contributor to neuronal degeneration. The accumulation of lactic acid from anaerobic glycolysis decreases the pH of the extracellular environment by elevating the concentration of H^+ ions, which induces acidosis and causes 'acidotoxicity', mediated by acid sensing ion channels (ASICs) that are abnormally more permeable to Na^+ and Ca^{2+} across the plasma membrane (Brouns et al. 2008; Ding et al. 2000; Katsura et al. 1994; Park et al. 1999; Sherwood et al. 2011; Xiang et al. 2004; Xiong et al. 2004). Contributing greatly to increased levels of intracellular Na^+ and Ca^{2+} is the activation of glutamate receptors (Lai et al. 2014). Reduced levels of ATP following ischemia also impair glutamate reuptake by glutamate transporters in both neurons and glial cells and result in accumulation of glutamate at synapses, which activates α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate and NMDA receptors (Camacho and Massieu 2006; Rossi et al. 2000). Overactivation of glutamate receptors drives an additional influx of Ca^{2+} and Na^+ into the cytosol. Simultaneously, the increased Ca^{2+} influx initiates a series of signaling events that lead to metabolic derangements known as excitotoxicity (Bano et al. 2005; Jeffs et al. 2007; Li et al. 2007; Schwab et al. 2002). Increased levels of cytoplasmic and mitochondrial Ca^{2+} activate catabolic enzymes, particularly endonucleases that cleave DNA to cause apoptosis, and calpains which hydrolyze cytoskeletal, membrane-associated and signaling proteins (Aki et al. 2002; Buddle et al. 2003; Ling et al. 2002; Liu et al. 2004; Nakagawa and Yuan 2000; Neumar et al. 2001; Roberts-Lewis et al. 1994; Xu et al. 2009).

Oxidative Stress in Stroke

Another major mechanism that contributes to brain injury and infarct development following ischemic stroke is oxidative stress, whereby an amplified production of reactive oxygen species (ROS) inflicts cerebral tissue damage. Increased levels of cytosolic and mitochondrial Ca^{2+} are a major contributor toward the production of ROS (Starkov et al. 2004). The accumulation of Ca^{2+} ions through the mitochondrial calcium uniporter into the mitochondrial matrix reduces the transmembrane potential, which leads to formation of transition pores that permit electron leakage to occur resulting in excessive production of superoxide (Green and Kroemer 2004; Nieminen 2003; Triantafilou et al. 2013). Accumulation of cytosolic Ca^{2+} also triggers production of ROS via activation of protein kinase C and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Brennan et al. 2009; Kahles et al. 2010; Yoshioka et al. 2011). In addition, the translocation of cytosolic phospholipase A_2 (PLA_2) to the plasma membrane and the conversion of xanthine dehydrogenase to xanthine oxidase can be induced by cytosolic Ca^{2+}, with both enzymes generating oxygen radicals (Abramov et al. 2007; Al-Gonaiah et al. 2009; Ono et al. 2009). Increased levels of intracellular Ca^{2+} also contribute to the activation of neuronal and endothelial nitric oxide synthase (n/eNOS)

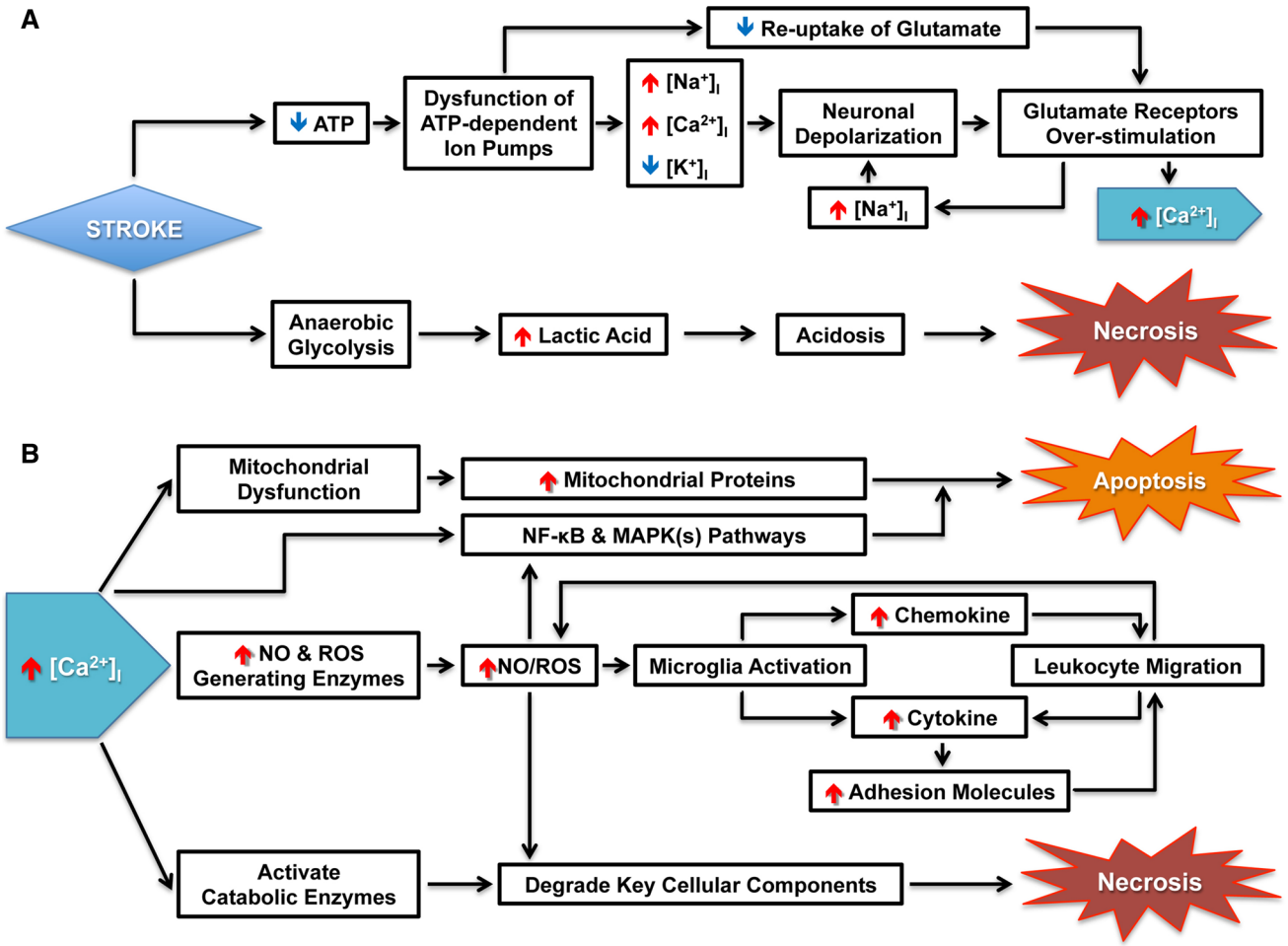

Fig. 1 Schematic diagram of biochemical events in ischemic stroke. The ischemic cascade is a series of interlinked biochemical events that occur during stroke, which includes bioenergetic failure, acidotoxicity, excitotoxicity, oxidative stress and inflammation. **a** In the event of a stroke, blood flow is reduced, and accordingly, the delivery of both oxygen and glucose to the brain becomes insufficient. Consequently, this either slows or suspends the production of ATP via oxidative phosphorylation inducing bioenergetic failure. Stroke bioenergetic failure induces widespread dysfunction of ATP-dependent ion pumps (e.g., Ca^{2+}-ATPase and Na^{+}/K^{+}-ATPase pumps) resulting in neuronal depolarization. As a consequence, voltage-gated Ca^{2+} channels will be opened and the influx of Ca^{2+} ions may result in uncontrolled glutamate release from presynaptic terminals. In addition, the ATP-dependent re-uptake of glutamate by glutamate transporters will be impaired due to energy failure. The accumulation of glutamate at synapses can activate glutamate receptors on neighboring neurons, driving a further influx of Ca^{2+} and Na^{+} ions into the cells. Unless energy supply is restored in time, these biochemical changes will initiate rapid necrotic excitotoxic cell death in neurons. Furthermore, the reduction of oxygen availability will initiate anaerobic glycolysis, which can lead to an increased production and accumulation of lactate within the ischemic tissue. The resultant accumulation of lactate will decrease intracellular pH (acidosis) causing acidotoxicity and necrotic cell death in the brain. **b** The increased concentration of Ca^{2+} ions in the cytosol within neurons can also activate catabolic enzymes, and ROS and NO generating enzymes causing mitochondrial dysfunction. ROS can activate the NF-κB and MAPK(s) signaling pathways, which can initiate apoptosis. The ROS that is produced can activate microglial cells causing increased production and release of pro-inflammatory cytokines. This can mediate cell damage by inducing cell adhesion molecule expression on endothelial cells and leukocytes to facilitate leukocyte infiltration into the ischemic region during reperfusion to release additional ROS and pro-inflammatory cytokines. Furthermore, microglial cells can release chemokines to guide the migration of additional leukocytes to the ischemic region inducing further damage. This figure and legend was adapted from a previous review article published by the authors (Fann et al. 2013a). *ATP* adenosine triphosphate, *I* intracellular, *NO* nitric oxide, *ROS* reactive oxygen species

and nitric oxide (NO) (Chan 2001; Heeba and El-Hanafy 2012; Nanetti et al. 2007). The augmented production of superoxide often leads to the formation of other ROS including hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^{-}), and peroxynitrite ($ONOO^{-}$; formed by the interaction of superoxide with NO). All of the above-mentioned ROS contribute to tissue damage via oxidation reactions with macromolecules including nucleic acids, proteins, carbohydrates and lipids (Lenaz 2012; Cabiscol et al. 2000; Adibhatla and Hatcher 2010; Shiva et al. 2004).

ROS can also activate signaling cascades that result in the transcription of proteins that mediate apoptosis. Overall, severe oxidative stress in the ischemic core region causes cell death through necrosis by damaging cellular components, while moderate oxidative stress in the ischemic penumbra can elicit apoptosis via inducing signaling cascades involving nuclear factor kappa B (NF-κB) directly, and mitogen-activated protein kinases (MAPKs) (in particular, the c-Jun-N-terminal kinase; JNK and p38 MAPK) (Barone et al. 2001; Chen et al. 2011; Kratsovnik et al. 2005; Ridder and Schwaninger 2009; Suzuki et al. 1997).

Inflammation in Stroke

Inflammation plays a major role in brain infarct development following stroke. Following the initiation of cerebral ischemia, local brain microglia are the first inflammatory cells to react. Experimental studies have proposed that microglia, activated by ROS during ischemia, are the foremost cause of secondary cell death in the penumbra region (Dirnagl et al. 1999; Danton and Dietrich 2003; Lai and Todd 2006). Nevertheless, many experimental studies have also shown that in response to oxygen deficiency, microglia are activated within minutes of ischemic stroke, even before any evident neuronal death has occurred (Nakajima and Kohsaka 2004). Another consequence following ischemic stroke is alterations in blood–brain barrier (BBB) permeability and vessel wall basal lamina structure. The extracellular matrix disruption is due to degradation of collagen type IV, laminin and fibronectin, and loss of BBB integrity by active matrix metalloproteases (MMPs), especially MMP2 and MMP9, and other proteases that are released from neurons and activated glial and endothelial cells (Rosenberg et al. 2001; Cunningham et al. 2005; Zhao et al. 2006; Planas et al. 2001).

We and others have established that cerebral ischemia also instigates activation of brain microvascular endothelial cells that leads to leukocyte contact with the endothelium via a process called tethering, mediated by adhesion molecules on the surfaces of endothelial cells and leukocytes. These adhesion molecules include intercellular adhesion molecule-1 (ICAM-1), P- and E-selectins, vascular cell adhesion molecules (VCAMs), and integrins, which have been shown to contribute to post-ischemic inflammation (Arumugam et al. 2004a; Ehrensperger et al. 2005; Huang et al. 2000; Yilmaz and Granger 2008; Zhang et al. 1998). Chemokines, for example macrophage inflammatory protein-1α, monocyte chemoattractant protein-1, and fractalkine play roles in guiding leukocytes as they migrate toward the injured ischemic brain region (Jin et al. 2013; Deshmane et al. 2009; Qin et al. 2014). Furthermore, recent studies have also shown that circulating lymphocytes ($CD4^+$ and $CD8^+$) that exhibit increased trafficking in the cerebral microcirculation following ischemia (Yilmaz et al. 2006) are also able to produce significant quantities of cytokines along with infiltrated neutrophils and macrophages that can induce an inflammatory phenotype in endothelial cells, astrocytes, oligodendrocytes and microglial cells (Arumugam et al. 2005; Yilmaz and Granger 2010). Several inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-18 and tumor necrosis factor (TNF) have been implicated in the pathogenesis of ischemic stroke. The production and release of pro-inflammatory cytokines, from infiltrated leukocytes as well as from activated cells in the brain parenchyma including neurons, oligodendrocytes, astrocytes, and microglial cells and microvascular endothelial cells, can lead to neuronal cell death (Allan and Rothwell 2001; Vila et al. 2000).

Additional Injury Mechanisms in Stroke

Recent studies have provided insight into additional molecular mechanisms of neuronal injury in stroke including the activation of complement cascades, inflammasomes and the hypoxisome (Fann et al. 2013a). Endogenous danger signals termed damage-associated molecular patterns (DAMPs) that are released by necrotic cells in the ischemic core may activate membrane receptors in neuronal and glial cells and may contribute to neuronal cell death and post-ischemic inflammation (Shichita et al. 2014). Complement cascade activation has been reported to be involved in ischemic brain injury via the production of several complement factors, including C1, C3a and C5a anaphylatoxins, that are involved in post-ischemic inflammation in neurons and glial cells (Arumugam et al. 2004b; Barnum et al. 2002; Gesuete et al. 2009; Leinhase et al. 2006; Van Beek et al. 2000). Our group recently established that activation of membrane receptors such as receptor for advanced glycation end products (RAGE) and toll-like receptors (TLRs) by DAMPs can lead to activation of NF-κB and MAPK(s) signaling pathways and consequent inflammasome activation (Fann et al. 2013a; Tang et al. 2007, 2013).

Inflammasomes are large multi-protein complexes in the cytosol that convert pro-caspase-1 into active cleaved caspase-1, which cleaves pro-IL-1β and pro-IL-18 into mature forms of IL-1β and IL-18 that are secreted into the extracellular environment (Fann et al. 2013a). In addition, cleaved caspase-1 can induce apoptosis as well as pyroptosis (Bergsbaken et al. 2009; Erener et al. 2012; Fink and Cookson 2006; Fink et al. 2008; Lamkanfi 2011; Sagulenko et al. 2013; Walsh et al. 2011; Zhang et al. 2003). There are a number of different inflammasomes that are known to contribute to neuronal cell death including

nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) Pyrin domain containing 1 (NLRP1) and NLRP3 inflammasomes (Abulafia et al. 2009; Deroide et al. 2013; Fann et al. 2013b; Iyer et al. 2009; Kono and Rock 2008; Legos et al. 2001; Li et al. 2009; Martinon et al. 2002; Savage et al. 2012; Tamatani et al. 2000). Recent research from our group also predicts that another multi-protein complex in the nucleus termed the hypoxisome (which includes Notch, NF-κB, HIF-1α, Pin1, c-Jun and p-53 proteins) may contribute to cell death following ischemic stroke (T. V. A. and D. G. J., unpublished findings).

Therapeutic Development for Stroke and Natural Products

Over the past four decades, abundant research has been conducted in an attempt to understand the underlying molecular mechanisms and to uncover the possibilities to reduce neuronal loss at the early stage of stroke onset. These include pharmacologically reducing infarct development and consequent neurological deficits. At present, there are a number of pharmacological agents that are considered to exert neuroprotective effects in experimental animal models of stroke (Baek et al. 2014; Yu et al. 2014; Li et al. 2014). Several neuroprotective agents have been evaluated in clinical trials for ischemic stroke treatment. Although the task of discussing these agents in detail is beyond the scope of this review, regrettably, most of these agents have failed to demonstrate therapeutic benefits using clinical endpoints (Grupke et al. 2015). These failures might be due to a number of factors including experimental design and execution of the trials, and in some cases the development of potentially serious side effects. By contrast, harnessing the therapeutic value of natural products is appealing given their good safety and tolerability, and expanding experimental and epidemiological data to support their roles to modulate the adaptive stress response signaling pathways and neuroprotective mechanisms following an ischemic insult (Trewavas and Stewart 2003; Mattson and Cheng 2006; Lee et al. 2014).

Natural medicinal products, defined as compounds derived from natural sources such as microbes, plants and animals, possess biological activities that have been harnessed (either in semi-pure or crude extract forms) for health benefits for thousands of years (Wang et al. 2007; Harvey 1999; Grabley and Thiericke 1999; Ji et al. 2009). Most commonly semi-pure or crude extracts of plants were used to treat human diseases. Recent advances in our understandings of receptor biology and pathophysiological mechanisms of diseases, and methods for purification of specific chemicals from extracts, have led to novel approaches for isolating and screening natural products (Berdy 2012; Atanasov et al. 2015). Early isolation of pure compounds from natural products occurred over 200 years ago when morphine was isolated from poppies (Corson and Crews 2007; Felter and Lloyd 1898; Hosztafi 1997; Kaiser 2008; Sneader 2005; Zenk and Juenger 2007). Similarly, well-known natural compounds such as salicin from willow bark and penicillin from microbial sources were isolated (Atanasov et al. 2015; Levesque and Lafont 2000; Fleming 1946). Consequently, significant efforts by the pharmaceutical industry to isolate pure and target-specific natural compounds with therapeutic effects were undertaken, which resulted in the development of 30 % of FDA-approved drugs (Newman and Cragg 2012). In the following sections, we focus on studies of phytochemicals that are emerging as potential therapeutic interventions for ischemic stroke.

Phytochemicals

Plants, such as vegetables and fruits, are known to contain chemicals that display many beneficial effects including stimulating adaptive cellular stress responses (hormesis), free radical-scavenging activities, anti-inflammatory activities, anti-cancer effects and direct neuroprotective effects (Slavin and Lloyd 2012; Joshipura et al. 2001; Gillman et al. 1995; Bradbury et al. 2014). Some of these chemicals from plants, also known as phytochemicals, have been shown to protect against ischemic stroke in experimental models by directly targeting the above-mentioned pathways (Fig. 2).

Most phytochemicals produced by plants fall within three chemical groups, namely, alkaloids, phenolics and terpenoids (Murugaiyah and Mattson 2015). While alkaloids play a role as substances that dissuade insects and herbivores, phenolics have multiple adaptive roles with herbivores and symbiotic organisms (Murugaiyah and Mattson 2015). Phenolics, which encompass at least one aromatic ring with one or more hydroxyl groups attached, are classified as either flavonoids or non-flavonoids (Del Rio et al. 2013). In excess of four thousand flavonoids have been identified in plants, the catalog continues to grow (Harborne and Williams 2000). Based on their structure, flavonoids can be subdivided into six different classes including: flavonols, flavones, flavanones, isoflavones, anthocyanidins and flavanols (D'Archivio et al. 2007). However, the non-flavonoids are composed of phenolic acids, phenolic alcohols, stilbenes and lignans (D'Archivio et al. 2007). On the other hand, a third group of plant phytochemicals, terpenoids, has a broad range of functions including abilities to behave as an attractant or a repellent (Murugaiyah and Mattson 2015).

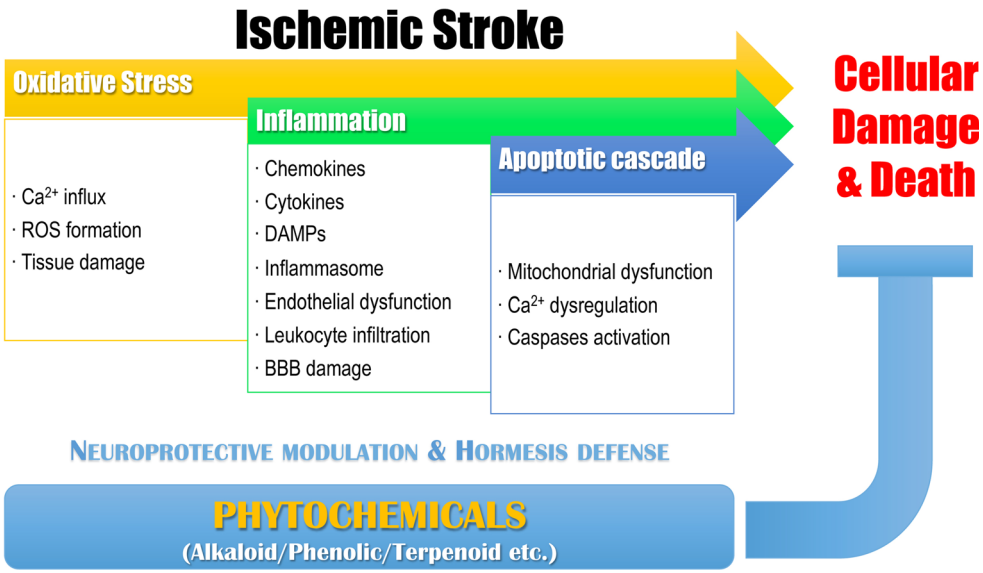

Fig. 2 Protective mechanisms of phytochemicals in stroke. The combination of oxidative stress, inflammation and apoptotic cell death cascades lead to bioenergetic failure and brain damage in ischemic stroke. Phytochemicals produced by plants are largely categorized as alkaloids, phenolics and terpenoids. Many of the pharmacological effects of phytochemicals are derived from hormesis effects in which adaptive stress response effectors are up-regulated including anti-oxidant enzymes, protein chaperones, growth factors, cytokines, calcium regulating proteins and mitochondrial proteins. Phytochemicals can reduce the stroke damage by suppression of oxidative stress and inflammation. Furthermore, phytochemicals can reduce the apoptotic cell death by modulating calcium influx and caspase cascades. *BBB* blood–brain barrier, *DAMPs* damage-associated molecular patterns, *ROS* reactive oxygen species

Phytochemicals That Suppress Oxidative Stress

Hormesis is an adaptive response of cells and organisms to a moderate physiological stress, toxin or chemical. Hormetic effects of phytochemicals are well established from previous research (Mattson 2008a). Numerous evidence in animal and human studies shows that phytochemicals may activate stress response pathways in cells at relatively low doses without adversely affecting their function (Mattson 2008b). These stress response effectors include, but are not limited to: anti-oxidant enzymes; protein chaperones; growth factors; cytokines; calcium regulating proteins; and mitochondrial proteins (Calabrese et al. 2010). Several phytochemicals have been shown to bolster endogenous anti-oxidant defenses. For example, several widely ingested phytochemicals activate nuclear factor (erythroid-derived 2)-like 2 (Nrf-2; a transcription factor) and its gene targets that are regulated by the anti-oxidant response element (ARE) DNA sequence. Activation of the Nrf-2/ARE pathway induces the production of anti-oxidant enzymes such as NAD(P)H dehydrogenase [quinone] 1 (NQO1) and heme oxygenase-1 (HO-1). Piceatannol, brazilin, sulforaphane, curcumin, epigallocatechin gallate (EGCG), baicalein, resveratrol and quercetin are examples of phytochemicals that activate Nrf-2/ARE-dependent anti-oxidant pathways in a variety of cell types including neural cells (Thakur et al. 2014; Wung et al. 2006; Choi and Kim 2008; Ernst et al. 2011; Murugaiyah and Mattson 2015).

There are some phytochemicals, such as curcumin, resveratrol and quercetin, that can increase the expression of protein chaperones including heat-shock proteins (HSPs), and growth factors encompassing brain-derived neurotrophic factor, insulin-like growth factor (IGF) and fibroblast growth factor (FGF) (Son et al. 2008; Mathers et al. 2004; Mattson et al. 2004; Young et al. 2004; Murakami 2013). Protein chaperones function by binding to and protecting other proteins and mediate the unfolded protein response in the endoplasmic reticulum that occurs in neurons in ischemic stroke (Lindholm et al. 2006; DeGracia and Montie 2004). The HSP response is a significant intracellular defense mechanism against ischemic stroke-induced stress conditions (Sharp et al. 2013). HSPs assist in protein protection, refolding, intracellular protection from protein damage, and also in the removal of aggregated proteins and impeding apoptotic cell death cascades (Wiegant et al. 2012). Examples of HSPs up-regulated in tissues following phytochemical consumption in animals and humans include HSP60, HSP70 and HSP90, as well as glucose-regulated proteins (GRP) 78 and 94 (Calabrese et al. 2012; Ohnishi et al. 2013).

Phytochemicals Can Suppress Inflammation

Phytochemicals are able to induce the expression of several growth factors and cytokines (Hur et al. 2012; Brown and Hampton 2011; Hirai et al. 2010; Moosavi et al. 2016;

Fernando et al. 2015). Growth factors are important for the maintenance, regeneration and survival of cells, with neurotrophins such as nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) as well as IGFs and FGF2 promoting the survival of neurons in response to stress (Venkatesan et al. 2015; Cheng et al. 1994b). Reduced expression of neurotrophins following ischemic stroke has been associated with a poor outcome (Wu 2005; Endres et al. 2003). Neurotrophins activate receptors and intracellular signaling cascades to enhance cell survival by activating transcription factors such as CREB that induce the expression of anti-apoptotic proteins such as B cell lymphoma 2 (Bcl-2) (Kitagawa 2007; Finkbeiner 2000). Phytochemicals can modulate the master switch for proinflammatory genes, NF-κB, and up-regulate the expression levels of several stress-responsive cytokines, which can exert beneficial effects by some of the above-mentioned hormesis-based mechanisms. For example, phytochemicals shown to increase TNF and IL-1β, while these proinflammatory cytokines known to contribute to injury mechanisms and post-stroke inflammation following cerebral ischemia, at lower concentration, they may play a pivotal role against neuronal stress (Cheng et al. 1994a). Indeed, it was previously reported that hippocampal neurons of mice lacking TNF receptors exhibit a suppressed cellular stress response and increased vulnerability to the excitotoxin kainic acid (Bruce et al. 1996), suggesting that endogenous TNF protects neurons by a hormesis-based mechanism. Similarly, some phytochemicals capable of inducing TNF and receptor stimulation may lead to the activation of the NF-κB signaling pathway in order to stimulate the expression of Mn-SOD and Bcl-2 to help neurons resist stress (Arumugam et al. 2006). These findings suggest that some cytokines induced by stress may mediate beneficial effects on the nervous system. On the other hand, the anti-oxidative and anti-inflammatory effects of phytochemicals on microglia and immune cells are reflected in reduced intracellular ROS levels, and inhibition of inflammatory NF-κB signaling in pathological conditions such as ischemic stroke (Stevenson and Hurst 2007; Farooqui 2012).

Phytochemicals Can Protect Neurons Against Apoptosis

As described in "Introduction" section, the mechanisms of neuronal apoptosis following ischemic stroke involve excessive Ca^{2+} influx, depolarization of mitochondria and release of Ca^{2+} from the endoplasmic reticulum. Disturbed Ca^{2+} homeostasis together with mitochondrial stress leads to activation of calpains and opening of mitochondrial permeability transition pores (mPTP), release of cytochrome c and activation of the caspase pathway to induce apoptosis (Kalogeris et al. 2012). Studies using cancer cells have shown that phytochemicals can accumulate in mitochondria and promote cell death (Chandra 2013). However, phytochemicals can also protect against both calcium dyshomeostasis and mitochondrial dysfunction in neuronal cells under stressful conditions (Lee et al. 2014). The differential effects of phytochemicals on mitochondrial function are determined by the concentration and nature of phytochemical, as well as the cell type and target organ. Mitochondrial uncoupling to a certain degree can be neuroprotective (Chan et al. 2006; Liu et al. 2006), and phytochemicals that stimulate mitochondrial uncoupling may initiate protective effects on neurons (Mattiasson et al. 2003; Lagouge et al. 2006; Pu et al. 2013). Other major hormesis pathways triggered by phytochemicals include the histone deacetylases of the sirtuin family and forkhead transcription factor family O (FOXO) transcription factors. FOXO transcription factors are activated in response to a wide range of external stimuli including growth factors, reduced nutrient levels and oxidative stress, and they up-regulate genes involved in energy metabolism and anti-oxidant pathways (Cameron et al. 2008; Frescas et al. 2005; Robb et al. 2008). Phytochemicals may be able to directly associate with SIRT1, a histone deacetylase, resulting in the activation of FOXO3 (Frescas et al. 2005). Activation of SIRT1 and other members from the sirtuin family can stimulate neuronal survival under neurodegenerative conditions (Brunet et al. 2004). It was observed that phytochemicals are able to induce the activation of FOXO transcription factors, which may be involved in mediating the hormetic effects of neurotrophic factors (Son et al. 2008; Gan et al. 2005). Additionally, 5′-AMP-activated protein kinase (AMPK), a key regulator in energy metabolism and survival is able to be activated in response to external stimuli (Yang et al. 2010). Impairment of AMPK signaling during ischemic stroke is known to contribute to neuronal cell death (Li and Keaney 2010). Furthermore, AMPK activation controls fuel utilization, the initiation of fatty acid oxidation and glucose uptake (Lee et al. 2015; Yamauchi et al. 2002). Phytochemicals such as resveratrol, quercetin, epigallocatechin-3-gallate (EGCG) and berberine can activate AMPK signaling which can result in downstream activation of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha (PGC-1α). PGC-1α is a transcription coactivator that plays a dominant role in the regulation of cellular energy metabolism and stimulates mitochondrial biogenesis (Liang and Ward 2006). However, evidence for phytochemical-induced PGC-1α activation is not well established.

In the next section we focus on the mechanisms by which phytochemicals improve injury outcome in different models of ischemic stroke, in addition to analyzing the

current epidemiological data regarding phytochemicals and stroke in human populations.

Phytochemicals as Therapeutic Agents in Stroke

The most critical step in reducing ischemic brain injury is to re-establish the blood flow with the aid of thrombolytic drugs. tPA is a serine protease that catalyzes the activation of the zymogen plasminogen into an active protease, plasmin. In 1995, investigators at the National Institute of Neurological Disorders and Stroke (NINDS) published the results of a large clinical trial demonstrating the efficacy of intravenous recombinant tissue plasminogen activator (r-tPA) in the treatment of acute ischemic stroke that was approved by the FDA the following year. Currently, r-tPA remains the only approved pharmacological treatment for stroke although its widespread use is limited by a narrow therapeutic window and significant risk for intracranial hemorrhage (NINDS 1995; Frey 2005; Chapman et al. 2014).

Despite preclinical evidence suggesting that many potential agents are able to prevent or attenuate a series of cell death mechanisms leading to ischemic brain injury, there are no recognizable neuroprotective agents that are able to improve stroke outcome in humans. Many factors are responsible for the failure in the development of neuroprotective therapeutics in stroke. Some of the possible reasons include but are not limited to the heterogeneity of human stroke, the anatomical and physiological differences between animal and human brains, the control of physiological variables in experiments, the difference in evaluating the efficacy of compounds in animal stroke models and the long post-stroke delay in the administration of drugs in clinical trials, in addition to, the limitation in clinical trials to test the combination of therapeutics for multi-target mechanisms. Recently, many experimental studies revealed that natural products, including phytochemicals, could aid not only to function as thrombolytic agents but also to offer further protection by reducing the extent of inflammatory and oxidative damage in neurons.

Anti-thrombotic Phytochemicals in Ischemic Stroke

Drugs for treating thrombosis can be divided into three categories: (1) anti-coagulants, which inhibit the coagulation system and interfere with further plaque expansion; (2) anti-platelet agents, which decrease platelet aggregation and inhibit thrombus formation; and (3) fibrinolytic drugs, which dissolve the formed thrombus directly (Ringleb 2006). Among these categories, fibrinolytic drugs are being evaluated as possible treatments for ischemic stroke. Fibrinolytic agents can be further classified into two groups: (1) plasmin-like proteases that directly hydrolyze fibrin and (2) plasminogen activators (e.g., tPA) (Li et al. 2007).

While there are many natural products showing strong anti-thrombotic effects, such as lumbrokinase from the artificial breeding earthworm in Japan (Mihara et al. 1983, 1991), nattokinase produced in the fermentation process of *Bacillus natto* or *Bacillus subtilis* var. *natto* (Sumi et al. 1987), subtilisin DFE from the supernatant of *Bacillus amyloliquefaciens* DC-4 culture broth (Peng et al. 2003), *Cordyceps sinensis* (Berk.) Sacc., which is a parasitic fungus of *Lepidoptera larvae* (Li et al. 2007), only a few phytochemicals are included in this category.

Several epidemiological studies revealed that cardiovascular disease risk is lower for people who drink low to moderate amounts of red wine than for people who do not drink at all (de Gaetano et al. 2002; Chiva-Blanch et al. 2013; Katsiki et al. 2014; Hansen et al. 2005). While these studies suggest that there is a reliable, noteworthy beneficial effect from moderate wine consumption, they failed to pinpoint specific phytochemicals that may be responsible for these beneficial effects.

In a preclinical study, it was shown that polyphenols in Armagnac extracts are capable of reducing arteriovenous shunt thrombosis in vivo in rats (Umar et al. 2003). The biologically active compound in Armagnac extracts is unclear as the extract was devoid of ellagic acid and ellagitannins, and the polyphenol-rich fraction was inactive (Al Awwadi et al. 2007). Thiosulfinates are characteristic flavors of Allium vegetables (garlic and onions), which were shown to inhibit platelet aggregation through calpain-dependent mechanisms (Badol et al. 2007). In activated platelets, thiosulfinates noticeably inhibited Ca^{2+} mobilization, calpain-induced synaptosomal-associated protein 23 (SNAP-23) cleavage and granule release. At the platelet surface, thiosulfinate, dose-dependently increased the basal level of free sulfhydryls, which contributed to their anti-aggregating property. *Jatropha gossypiifolia* L. (Euphorbiaceae) is a medicinal plant, the leaves of which are being consumed for their anti-thrombotic effects. The aqueous crude leaf extract and residual aqueous fraction possesses significant anti-coagulant and anti-oxidant activities without cytotoxic effects in vitro (Felix-Silva et al. 2014). However, this study failed to identify the active phytochemicals in the leaf extract. Another example comes from a study showing fibrinolytic activity as well as blood plasma cholesterol and triglyceride lowering effects of fresh and self-fermented pine needle (*Pinus densiflora* Sieb. Et Zucc.) extracts (Park et al. 2008). Finally, several flavonoid glycosides isolated from the grains of *Sorghum bicolor* L. exhibited potential anti-coagulation effects (Nguyen et al. 2014). It will be of considerable interest to determine whether such phytochemicals with anti-clotting and/or fibrinolytic activity are beneficial when used alone

or in combination with r-tPA or other agents in ischemic stroke.

Anti-inflammatory Phytochemicals in Ischemic Stroke

Clinical and experimental studies have demonstrated a fundamental relationship between systemic inflammation and ischemic brain injury. Many experimental studies have shown that therapies targeting inflammatory cascades attenuate the growth of brain infarction and improve neurological outcomes following ischemic stroke. Over the years, many phytochemicals have been shown to promote brain repair following experimental ischemic stroke by targeting inflammatory mechanisms (Table 1). We have summarized below some of the phytochemicals that have been shown to protect against ischemic brain injury by targeting various inflammatory mechanisms.

Intravenous injection of theaflavin, a constituent of black tea, inhibited leukocyte infiltration and expression of ICAM-1, cyclooxygenase-2 (COX-2) and inducible NOS (iNOS) in injured brain and reduced infarct size and edema volume, at least in part by reducing the phosphorylation of signal transducer and activator of transcription (STAT)-1 (Cai et al. 2006). Another study also confirmed the anti-inflammatory effect of theaflavin in an ischemic stroke model by showing decreased nuclear localization of NF-κB, and preservation of kappa B inhibitor (IκB) in the cytoplasm (Cai et al. 2007).

Apigenin, a flavonoid found in many kinds of plants, has been shown to reduce the expression of iNOS and COX-2 in microglia and decrease the production of NO and prostaglandin E_2 (PGE_2) under in vitro ischemia-like conditions (Ha et al. 2008). In addition, apigenin suppressed p38 MAPK, JNK phosphorylation, increased Mn-SOD content and phosphorylation levels of STAT3, which synergistically elevated its anti-oxidant activity to protect neuronal cells from injury in a middle cerebral artery occlusion (MCAO) reperfusion model (Ha et al. 2008; Cai et al. 2016).

Pinocembrin is one of the primary flavonoids isolated from a variety of plants, but mainly from heartwood of pine trees. Gao et al. (2010) reported that intravenous injection of pinocembrin in a dose range of 3–30 mg/kg at 0, 8 or 16 h after ischemic stroke reduced pro-inflammatory cytokines such as TNF, IL-1β, endothelial and leukocyte adhesion molecules—ICAM-1, VCAM-1 and iNOS. In addition, pinocembrin inhibited the activation of both microglia and astrocytes and down-regulated the expression of endothelial MMPs.

Intravenous injection of silymarin (1–10 μg/kg), a bioactive component isolated from *Silybum marianum*, reduced the expression of NF-κB and inflammatory proteins such as iNOS, COX-2 and myeloperoxidase (MPO), as well as production of the pro-inflammatory cytokines TNF and IL-1β (Hou et al. 2010). Another bioactive component isolated from *Silybum marianum*, silibinin, also significantly reduced pro-inflammatory NF-κB activity in ischemic brain tissue after experimental stroke (Wang et al. 2012). Both silymarin and silibinin alleviated not only the production of inflammatory cytokines but also reduced infarct volume, suppressed brain edema and neurological deficit following ischemic stroke. Similarly, treatment with chrysin, a naturally occurring flavonoid found in *Passiflora caerulea*, *Passiflora incarnata*, and *Oroxylum indicum*, significantly ameliorated ischemic stroke-induced up-regulation of NF-κB, COX-2 and iNOS (Yao et al. 2014).

Our group recently demonstrated anti-inflammatory effects of the flavonoid fisetin (3,3′,4′,7-tetrahydroxyflavone) in an ischemic stroke model (Gelderblom et al. 2012). Fisetin has been shown to improve stroke injury outcome evaluated 24 h after experimental stroke when given 5 min (Maher et al. 2007) or 30 min after induction of ischemia (Rivera et al. 2004). Our study showed even 3 h after the onset of ischemia, fisetin treatment reduced infarct size by 35 % (Gelderblom et al. 2012). As explained in "Pathophysiology of Stroke" section, infiltrating immune cells significantly contributes to post-stroke inflammation and infarct development. Fisetin not only inhibited the infiltration of macrophages and dendritic cells into the ipsilateral brain, but also suppressed local immune cell activation (Gelderblom et al. 2012).

Another well-known phytochemical that possesses anti-inflammatory effects is quercetin. Quercetin is a common dietary flavone existing in onions, broccoli, leafy green vegetables and medicinal herbs with multiple bioactivities. A recent study showed an anti-inflammatory neuroprotective effect of quercetin by down-regulating iNOS in an animal model of ischemic stroke (Ghosh et al. 2013).

Resveratrol has been suggested to be the central phytochemical responsible for the anti-aging effect of red wine which also exhibits neuroprotective effects by targeting inflammatory mechanisms. While many studies have reported neuroprotective effects of resveratrol in stroke, only a few studies investigated its anti-inflammatory mechanisms. Anti-inflammatory mechanisms of resveratrol in stroke include reduced expression of pro-inflammatory cytokines such as IL-6 (Wang et al. 2001) and TNF (Orsu et al. 2013), diminished MMP-9 (Gao et al. 2006), reduced iNOS mRNA and protein levels (Tsai et al. 2007) and reduced expression of vascular adhesion molecules that promote leukocyte infiltration (Orsu et al. 2013).

Phytoestrogens are chemicals structurally similar to estrogen that are found in plant foods such as beans, seeds and grains, and exhibit anti-inflammatory effects in

Table 1 Anti-inflammatory phytochemicals for the treatment of stroke

Phytochemical	Origin	Mode of study	Possible mechanisms	References
Apigenin	N/A	In vitro; in vivo (Mouse)	Cytokine reduction; p-p38 and p-JNK inhibition	Ha et al. (2008)
Astragaloside IV	*Astragalus membranaceous*	In vivo (Rat)	Neutrophil infiltration inhibition; cytokine reduction; NF-κB pathway inhibition	Li et al. (2012)
Chrysin	Propolis	In vivo (Mouse)	Cytokine reduction; NF-κB pathway inhibition	Yao et al. (2014)
Crataegus flavonoids	*Crataegus pinnalifida*	In vivo (Gerbil)	NO inhibition; cytokine reduction; NF-κB pathway inhibition	Zhang et al. (2004)
Danshensu	*Salvia miltiorrhiza*	In vivo (Rat)	Bcl-2 and p-GSK-3β and p-AKT up-regulation; Bax inhibition; caspase inhibition	Guo et al. (2015)
Ferulic acid	N/A	In vivo (Rat)	Thioredoxin-ASK1 interaction reduction (anti-apoptosis)	Sung et al. (2014)
Fisetin	N/A	In vitro; in vivo (Mouse)	Immune cells suppression; cytokines reduction; NF-κB pathway inhibition	Gelderblom et al. (2012)
Ginsenoside Rb1	*Panax ginseng*	In vivo (Rat)	Microglia suppression; cytokine reduction; NF-κB pathway inhibition	Zhu et al. (2012)
Ginsenoside Rd	*Panax ginseng*	In vivo (Rat, Human)	Microglia suppression; cytokine reduction; positive clinic outcome	Ye et al. (2011) and Liu et al. (2012a, b)
Huperzine A	*Huperzia serrata*	In vivo (Rat)	Immune cells suppression; cytokine reduction; NF-κB pathway inhibition	Wang et al. (2008)
Leonurine	*Herba leonuri*	In vivo (Rat)	Mitochondrial stabilization; Bcl-2 up-regulation; Bax inhibition	Qi et al. (2010)
Luteolin	N/A	In vivo (Rat)	TLR inhibition; NF-κB pathway inhibition; p-p38 inhibition; p-ERK1/2 activation	Qiao et al. (2012)
Pinocembrin	Propolis	In vivo (Rat)	Cytokine reduction; MMP inhibition	Gao et al. (2010)
Quercetin	N/A	In vivo (Rat)	Cytokine reduction; caspase inhibition	Ghosh et al. (2013)
Resveratrol	N/A	In vivo (Rat)	Cytokine reduction; NO inhibition; Bcl-2 up-regulation	Tsai et al. (2007) and Orsu et al. (2013)
Ruscogenin	*Ophiopogon japonicus*	In vivo (Mouse)	Cytokine reduction; NF-κB pathway inhibition	Guan et al. (2013)
6-Shogaol	*Zingiber officinale*	In vitro; in vivo (Rat)	Microglia suppression; caspase inhibition; Cytokine reduction	Ha et al. (2012)
Silibinin	*Silybum marianum*	In vivo (Rat)	p-Akt and p-mTOR up-regulation; NF-κB pathway inhibition	Wang et al. (2012)
Silymarin	*Silybum marianum*	In vivo (Rat)	Cytokine reduction; NO inhibition; NF-κB pathway inhibition; STAT-1 reduction	Hou et al. (2010)
Sinomenine	*Sinomenium acutum*	In vitro; in vivo (Rat)	Bcl-2 up-regulation; Bax inhibition; caspase inhibition	Wu et al. (2011)
Tetrahydroxystilbene	*Polygonum multiflorum*	In vitro; in vivo (Mouse)	Bcl-2 up-regulation; Bax and p-JNK inhibition; NO inhibition	Wang et al. (2009)
Tetramethylpyrazine	*Ligusticum wallichii*	In vivo (Rat)	Immuncells suppression; cytokine reduction; p-JNK inhibition	Kao et al. (2013)
Theaflavin	Black tea	In vivo (Rat)	Cytokine reduction; p-STAT-1 reduction	Cai et al. (2006)
Ursolic acid	N/A	In vivo (Mouse)	TLR4 inhibition; NF-κB pathway inhibition	Li et al. (2013)

N/A not specified in the article

ischemic stroke (Burguete et al. 2006; Schreihofer and Redmond 2009). The phytoestrogen genistein exhibited neuroprotective effects following ischemic stroke in rats by targeting the NF-κB signaling and possibly by inhibiting downstream inflammatory immune cells in the brain (Aras et al. 2015).

Cinnamophilin, a thromboxane A2 antagonist isolated from *Cinnamomum philippinense*, exhibits neuroprotection against ischemic stroke in animal models possibly by inhibiting inflammatory pathways (Lee et al. 2005, 2009).

Other phytochemicals that have been shown to exhibit anti-inflammatory effects in ischemic stroke models

include: ginsenoside Rb1 and ginsenoside Rd, found in the plant genus *Panax* (ginseng) (Zhu et al. 2012; Nabavi et al. 2015; Ye et al. 2009, 2011; Liu et al. 2012b); puerarin, an isoflavone enriched in *Pueriae Radix* (Gao et al. 2009; Lim et al. 2013); ruscogenin, enriched in Chinese herb *Ophiopogon japonicas* (Guan et al. 2013); astragaloside IV, a purified small molecular weight saponin from *Astragalus membranaceus* (Qu et al. 2009); 6-shogaol, a ginger terpenoid (Ha et al. 2012), tetrahydroxystilbene and a major compound in Chinese herb *Polygonum multiflorum* (Wang et al. 2009); huperzine A, a representative compound from *Huperzia serrate* (Wang et al. 2008); sinomenine from *Sinomenium acutum* (Wu et al. 2011; Qian et al. 2007); tetramethylpyrazine, enriched from *Ligusticum wallichii* Franchat (Chuan Xiong) (Kao et al. 2013); ursolic acid, a natural pentacyclic triterpenoid acid (Li et al. 2013); and crataegus flavonoids extracted from the leaves of the *Crataegus Pinnalifida* Bge (hawthorn) (Zhang et al. 2004). This wide range of phytochemicals that can suppress neuroinflammation suggests considerable potential for their applications in stroke therapy.

Neuroprotective Phytochemicals in Ischemic Stroke

Neuroprotective approaches that curtail primary ischemic and reperfusion-induced neuronal cell death and tissue loss have been identified in animal models of ischemic stroke. However, in instances where a particular compound that appeared promising in animal models was evaluated in stroke patients, clinical efficacy was not observed. Over the years, many phytochemicals have been found to act directly on neurons to protect them against simulated ischemia in culture, ameliorate neuronal degeneration and improve functional outcome in animal models of stroke. In this section we describe neuroprotective phytochemicals in experimental models relevant to ischemic stroke (Table 2). These phytochemicals may target multiple injury mechanisms following ischemic stroke. However, in order to improve readability, we have categorized the phytochemicals with regard to their proposed major mechanism of action.

Anti-oxidant phytochemicals

Our group has shown that neuroblastoma cells and primary cortical neurons exposed to *Plumbagin*, a chemical found in the plant genus *Plumbago* as well as in carnivorous plant genera *Drosera* and *Nepenthes*, provides protection against subsequent oxidative and metabolic insults (Son et al. 2010). The administration of plumbagin significantly reduced the amount of brain damage and improved neurological deficits in a rodent model of focal ischemic stroke (Son et al. 2010). In addition, we investigated the mechanisms responsible for the anti-oxidant effects of plumbagin and found that it specifically activates the Nrf2/ARE pathway resulting in the up-regulation of target genes such as HO-1, thioredoxin reductase 1, NQO1, glutamate-cysteine ligase modifier subunit (GCLM), and glutathione-*S*-transferase 1 (GST). Plumbagin also increases the phosphorylation (activation) of AKT and ERK-1,2 (p42/p44 MAP) kinases. These effects of plumbagin increase resistance of neurons to oxidative insults in culture and to ischemic stroke in vivo (Son et al. 2010).

Totarol, is a phenolic diterpenoid and a major ingredient found in the sap of *Podocarpus totara*, exhibits anti-oxidative and neuroprotective actions in stroke models (Gao et al. 2015). Totarol prevented neuronal death in ischemic conditions by increasing the phosphorylation of Akt and GSK-3β phosphorylation, expressions of Nrf2 and HO-1 as well as by promoting GSH and SOD activities (Gao et al. 2015).

Kolaviron is a mixture of flavonoids extracted from the seeds of Garcinia kola, which has abundant beneficial effects against a number of diseases. Pre-treatment with kolaviron significantly improved anti-oxidant activities by increasing glutathione levels and increasing the activities of anti-oxidant enzymes (Akinmoladun et al. 2015). In addition, kolaviron is possibly involved in electrolyte homeostasis, anti-inflammatory and anti-excitotoxic mechanisms.

Leonurine, a main bioactive component from *Herba leonuri*, shows therapeutic potential for cardiovascular diseases and stroke prevention. It was shown that animals pre-treated with leonurine orally for 7 days, had reduced infarct volume and improved neurological deficits compared to control groups (Loh et al. 2010). Leonurine-treated animals displayed increased activities of the anti-oxidant enzymes, SOD and glutathione peroxidase, whereas the lipid peroxidation marker, malondialdehyde, and mitochondrial ROS production were decreased. Further studies have confirmed the effect of leonurine against stroke-induced brain injury, by showing that leonurine increased activities of SOD, CAT and UCP4, and decreased ROS levels in the mitochondria isolated from the ischemic cortex (Qi et al. 2010; Liu et al. 2012a).

Luteolin, enriched in *Ixeris sonchifolia*, activates Nrf-2-dependent transcription of HO-1 and exhibits neuroprotection against ischemic stroke. Luteolin significantly increased the activities of SOD1, CAT, Bcl-2 and claudin-5, and alleviated neurological deficits, infarct volume and brain water content (Zhang et al. 2013b). In addition, downregulation of TLR-4, TLR-5, NF-κB and p38 MAPK, and upregulation of ERK expression were also observed following luteolin treatment in an ischemic stroke model (Qiao et al. 2012).

There are many reports on neuroprotective effects of plant extracts, which are likely to contain phytochemicals

Table 2 Anti-oxidative and neuroprotective phytochemicals for the treatment of stroke

Phytochemical	Origin	Mode of study	Possible mechanisms	References
Apigenin	*Clematis tangutica*	In vitro; in vivo (Mouse)	ROS reduction; STAT-3 up-regulation	Cai et al. (2016)
Cinnamophilin	*Cinnamomum philippinense*	In vitro; in vivo (Rat)	ROS reduction	Lee et al. (2009)
Genistein	Soy extract	In vitro; in vivo (Rat)	ROS reduction; Nrf1 up-regulation; caspase inhibition	Linford and Dorsa (2002) and Aras et al. (2015)
Ginsenoside Rd	*Panax ginseng*	In vitro	ROS reduction; MMP preservation	Ye et al. (2009)
Ginsenoside Rg1	*Panax ginseng*	In vitro; in vivo (Rat)	Caspase inhibition; calcium influx inhibition	Zhang et al. (2008)
Ginsenoside Rg3	*Panax ginseng*	In vivo (Rat)	ROS reduction; MPTP formation inhibition;	Tian et al. (2005, 2009)
Hyperforin	*Hypericum perforatum*	In vivo (Rat)	TRPC6 up-regulation; p-CREB up-regulation	Lin et al. (2013)
Kolaviron	*Garcinia kola*	In vivo (Rat)	ROS reduction	Akinmoladun et al. (2015)
Leonurine	*Herba leonuri*	In vivo (Rat)	ROS reduction; Bcl-2 and UCP4 up-regulation; Bax inhibition	Loh et al. (2010) and Liu et al. (2012a, b)
Ligustilide	*Angelica sinensis*	In vivo (Mouse)	ROS reduction; Bcl-2 up-regulation; Bax and caspase inhibition	Kuang et al. (2006)
Luteolin	*Ixeris sonchifolia*	In vitro; in vivo (Rat)	ROS reduction; Nrf2 up-regulation; caspase inhibition	Zhang et al. (2013a, b)
Plumbagin	N/A	In vitro; in vivo (Mouse)	Nrf2/ARE pathway activation; HO-1 up-regulation	Son et al. (2010)
Puerarin	*Pueriae lobata*	In vivo (Rat)	Erythropoietin activation	Gao et al. (2009)
Resveratrol	Grape/Wine	In vivo (Mouse)	MMP reduction; Bcl-2 up-regulation; Bax inhibition	Gao et al. (2006) and Li et al. (2012)
Spiramine T	*Spiraea japonica*	In vivo (Gerbil)	ROS reduction	Li et al. (2001)
Totarol	*Podocarpus totara*	In vitro; in vivo (Rat)	ROS reduction; Akt and GSK-3beta up-regulation; Nrf2 up-regulation	Gao et al. (2015)

N/A not specified in the article

that effectively target oxidative stress to protect the brain against stroke injury in animals. Examples of such neuroprotective plant extracts include: Gua-lou-gui-zhi decoction (TCM) that is comprised of six herbs (*Cinnamomum cassia* Presl., *Glycyrrhiza uralensis* Fisch., *Paeonia lactiflora* Pall., *Trichosanthes kirilowii* Maxim., *Zingiber officinale* Rosc. and *Ziziphus jujuba* Mill) (Zhang et al. 2015); Korean ginseng tea extract, prepared from the roots of *Panax ginseng* (Shah et al. 2005); and the root extract of the fern *Helminthostachys zeylanica* (L.) Hook. (Hsieh et al. 2015). These extracts may also provide neuroprotective effects by anti-inflammatory and anti-apoptotic mechanisms. Their active components are currently under investigation by many research groups around the world.

Anti-apoptotic phytochemicals

Targeting apoptotic mechanisms in order to save neurons in the penumbra have been pursued by many research groups. Anti-apoptotic agents such as the broad-spectrum caspase inhibitor z-VAD and peptide-based caspase inhibitors have been shown to obstruct neuronal damage in animal models of stroke (Woodruff et al. 2011). There are several phytochemicals that are effective against apoptotic cell death mechanisms in ischemic stroke. Genistein, an isoflavone soy derivative that binds to estrogen receptors, not only has anti-inflammatory properties, but also has potent anti-apoptotic activity. It was reported that 50 nM genistein treatment significantly reduced apoptosis in primary cortical neurons through an estrogen receptor-dependent mechanism (Linford and Dorsa 2002). An anti-apoptotic effect of genistein was also recently confirmed in in vivo models of ischemic stroke; apoptosis-related cysteine peptidase caspase-3 and caspase-9 levels were reduced along with oxidative stress markers, such as malondialdehyde, following treatment with genistein (Aras et al. 2015).

Hyperforin, a lipophilic constituent of the medicinal herb St. John's wort, can activate the transient receptor potential canonical 6 (TRPC6) channel and increase

phosphorylated CREB (p-CREB), and have antagonistic effects on the NMDA receptor (Kumar et al. 2006; Lin et al. 2013). Hyperforin, when applied immediately after induction of cerebral ischemia, significantly reduces apoptotic cell death and infarct development accompanied by decreased SBDP145 activity and elevated TRPC6 and p-CREB activity (Lin et al. 2013).

Spiramine T, an atisine-type diterpenoid alkaloid isolated from the Chinese herbal medicine *Spiraea japonica* var. acuta, exhibits neuroprotective effects by reducing calcium accumulation and lipid peroxidation and ultimately, reducing neuronal apoptosis (Li et al. 2001). In addition, there are a few plant extracts, such as those of *Hibiscus sabdariffa*, which show an anti-apoptotic effect against serum/glucose deficiency in cell culture experiments (Bakhtiari et al. 2015).

Until now, numerous phytochemicals and plant extracts have been investigated by research groups around the world for their protective role against stroke. It is very promising that many of these phytochemicals exist abundantly in various plant sources, which are consumed by humans without causing significant side effects. Moreover, some of the phytochemicals like ginsenosides possess multi-functional effects against diverse pathologic mechanisms of stroke. These characteristics of phytochemicals should be considered in the future development of therapeutics against stroke.

Phytochemicals and Stroke Risk Reduction

Tailoring a primary prevention strategy is another central idea in the combat against stroke. Data supporting a role for phytochemical-containing natural products in humans are borne mainly from epidemiological observations throughout the world. Large cohort studies have established that regular consumption of vegetables and fruits in diet is linked with reduced risk of age-related diseases, such as cardiovascular disease including stroke, neurodegenerative diseases and cancer (Bradbury et al. 2014; Joshipura et al. 2001; Slavin and Lloyd 2012). It is presumable that the phytochemicals in fruits and vegetables, as well as from other plant sources, may reduce the occurrence of ischemic stroke by attenuating key pathological processes contributing to stroke (Chen et al. 2012; McCullough et al. 2012; Larsson et al. 2013). The beneficial effects of fruit and vegetable intake on the risk of ischemic stroke were reported in a Danish (Johnsen et al. 2003) and a Japanese (Sauvaget et al. 2003) cohort study. In addition, Larsson et al. (2013) reported in a recent epidemiological study that consumption of vegetables and fruits, especially apples, pears and green leafy vegetables, is inversely associated with stroke occurrence.

In addition to the above observations, a Mediterranean-style diet, which is well known as one of the healthy lifestyle diets, was also reported to reduce the risk of cardiovascular events including ischemic stroke (Gardener et al. 2011). Furthermore, a separate study had suggested a protective role for high olive oil consumption, which is often observed in a Mediterranean-style diet, on the risk of stroke, especially in older subjects (Samieri et al. 2011).

Based on such observations, recent studies try to focus on specific components of such diets. Large Italian population (Del Rio et al. 2011) and Swedish women (Rautiainen et al. 2012) cohort studies concluded that total antioxidant capacity in diet is inversely correlated with stroke onset. Another cohort study by Chen et al. (2013a, b) revealed a significant inverse dose–response relationship between dietary fiber intake and the risk of stroke. Despite the accumulated compelling data, it still remains unclear which specific phytochemicals are most responsible for such protective effects on stroke incidence, and the kind of neuroprotective pathways that contribute to such protective effects of phytochemicals in food and vegetables. Further well-designed clinical trials examining the value of a regular intake of purified phytochemicals will be needed to investigate the relationship between phytochemicals and the prevention of ischemic stroke.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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