The Advances in Neurobiology

M. Ishwarya and R.T. Narendhirakannan

Abstract Neurological disorders are diseases of the brain, the spine, and the nerves that connect them. There are more than 600 diseases of the nervous system, such as brain tumors, epilepsy, Parkinson's disease, and stroke as well as less familiar ones such as frontotemporal dementia, Alzheimer's disease, and other dementias; cerebrovascular diseases including stroke, migraine, and other headache disorders; multiple sclerosis; neuroinfections; brain tumors; traumatic disorders of the nervous system such as brain trauma; and neurological disorders as a result of malnutrition. More than a decade of research worldwide has shown that berries support cognitive health by protecting nerves and help brain cells communicate with each other and improve the flexibility of nerve structures. Berries help nerves tolerate stress, including the stress of toxic exposure. They also support the healthy function of glial cells in the brain, essential for optimum brain function. Polyphenols, namely, anthocyanins, found in berries may slow cognitive decline through antioxidant and anti-inflammatory properties in experimental animals. Based on the previous reports, this review explains the beneficial effects of the phytochemicals present in nine varieties of berries on neurodegenerative diseases.

Keywords Berries • Neurodegenerative diseases • Neuroprotective • Natural products

Introduction

Neurological disorders are diseases of the central and peripheral nervous system (the brain, spine, and nerves that connect them). There are more than 600 diseases of the nervous system. These disorders include epilepsy; Alzheimer's disease and other dementias; cerebrovascular diseases including stroke, migraine, and other

M. Ishwarya • R.T. Narendhirakannan, Ph.D., F.I.S.C.A., D.C.S. (✉)
Department of Biotechnology, School of Biotechnology and Health Sciences,
(Karunya Institute of Technology and Sciences) Karunya University,
Karunya Nagar, Coimbatore 641 114, Tamil Nadu, India
e-mail: bionaren_phd@yahoo.co.in

M.M. Essa et al. (eds.), *The Benefits of Natural Products for Neurodegenerative Diseases*, Advances in Neurobiology 12, DOI 10.1007/978-3-319-28383-8_15

headache disorders; multiple sclerosis; Parkinson's disease; neuroinfections; brain tumors; traumatic disorders of the nervous system such as brain trauma; and many other neurological disorders.

Hundreds million people worldwide are affected by neurological disorders. Approximately 6.2 million people die because of stroke each year; over 80 % of deaths take place in low- and middle-income countries. More than 50 million people have epilepsy worldwide. It is estimated that there are globally 35.6 million people with dementia with 7.7 million new cases every year—Alzheimer's disease is the most common cause of dementia and may contribute to 60–70 % of cases. The prevalence of migraine is more than 10 % worldwide (WHO 2014).

Physical symptoms of neurological disorders that may sustain for a short-term or long-term duration include partial or complete paralysis, muscle weakness, loss of sensation, seizures, difficulty in vocabulary, poor cognitive abilities, and lack of alertness (Psychguides.com).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) play an important role in neurodegenerative disorders by oxidizing the macromolecules like proteins, DNA, and lipids leading to the common final pathway for cell death (Sohal et al. 1995). According to the study conducted by Andersen (2004) and Ramassamy (2006), it is evident that there was an increased level of ROS markers observed in tissues from patients with neurodegenerative disorders.

The excessive production of reactive oxygen species, nitric oxide, and tumor necrosis factors may initiate neuronal apoptosis (Iadecola et al. 1996; Chan 2001) after cerebral ischemia-reperfusion injury (White et al. 2000; Sugawara et al. 2014; Abas et al. 2010). Oxidative damage has been found in all classes of organic molecules that are critical for maintaining neuronal structure and function. Excessive lipid, protein, and DNA peroxidation have all been studied in neurodegenerative disorders (Smith et al. 2000).

There are more than 600 neurological disorders that strike millions of people each year. These diseases and disorders inflict great pain and suffering for millions of patients and their families.

Key Treatments Available for Neurodegenerative Diseases

Hybrid PET/MRI testing Brain mapping Cyber Knife Stem cell therapy (Lindvall and Kokaia 2006) Deep brain stimulationGamma Knife Parkinson's disease or epilepsy has shown a considerable effect in the treatment of attention deficit hyperactivity disorder (ADHD), anxiety and other mood disorders, and a range of primary psychogenic impairments (Tarazi et al. 2014; Fasano and Lozano 2015).

Epigenetics and Neurodisorders

The epigenetic changes in various neurological diseases, the first issue to consider is whether the normal course of maturation and aging is associated with changes in the brain's epigenome.

Age-related epigenetic drifts could impact vulnerability to neurodegenerative disease. For example, in the mouse cerebellum, the levels of the mC5 derivative, 5-hydroxymethyl-cytosine (5hmC), are subject to a tenfold increase from postnatal week 1 to adulthood. Notably, among the genes that are affected by increasing 5hmC amounts at their promoters during cerebellar maturation, pathways for age-related neurodegenerative diseases and angiogenesis were overrepresented and included at least 15 genes linked to hereditary forms of spinocerebellar ataxia, a neurological syndrome defined by severe motor dysfunction with the degeneration of cerebellar Purkinje neurons and other systems (Szulwach et al. 2011).

Drawbacks of Neurological Drugs

Many drugs can cause confusional states, including amphetamines, anticonvulsants, antidepressants, antituberculous drugs, antimalarials, anti-inflammatories, cardiac glycosides, diuretics, hypotensive agents, H2 antagonists, neuroleptics, opiates, sympathomimetics, and sedatives. Agitation and confusion may be part of a withdrawal syndrome from addiction of drugs or alcohol. Central neurotoxicity can result from chemotherapy (particularly methotrexate, cytarabine, and ifosfamide used in the treatment of acute leukemias) ranging from minor cognitive impairment to encephalopathy (Verstappen et al. 2003). Confusion, cognitive impairment, and hallucinations are manifestations of relatively reduced cholinergic activity. Antiparkinsonian medications, particularly anticholinergics and dopamine agonists, may induce such adverse effects that necessitate dose reduction although discontinuation is often required. Psychosis occurs more rarely. Ataxia, dysarthria, and nystagmus can be a consequence of phenytoin toxicity. Akathisia (restlessness) may be induced by antidepressants, antipsychotics, antihistamines, calcium channel blockers, carbamazepine, or metoclopramide (Grosset and Grosset 2004).

Neuroprotective Medicine from Natural Source

It is widely accepted that a healthy diet is an important factor in reducing the risk of several diseases including cardiovascular diseases (Willcox et al. 2003) and certain cancers (Giovannucci 1999) and development of age-related neurodegenerative diseases (Lau et al. 2005), as has been demonstrated in a large number of epidemiological studies. Vegetables and fruits are of great importance in the human diet as they provide a major source of bioactive substances. Polyphenols, ubiquitously present in them, have been considered as the major responsible elements for the beneficial effect observed (Arts and Hollman 2005). Higher consumption of components/nutrients with antioxidant capabilities has been associated with lower frequency of numerous human morbidities or mortalities as per many epidemiological studies (Bhandari and Kamdod 2012).

Role of Berries

Considering the limits of existing prevention methods, intervention strategies using antioxidant and flavonoid-rich natural products such as fruits, vegetables, and nuts are of paramount importance (Essa et al. 2012). Considerable research has been directed at the potential health benefits of eating berries. As well as being a good source of vitamin C, dietary fiber, and minerals, berries contain high levels of natural polyphenol components that act as potent antioxidants. Berry extracts, rich in polyphenols, have a range of biological effects that can have beneficial outcomes on human health (Battino et al. 2009).

Active Compounds in Berries

1	Tomato (*Solanum lycopersicum*)	Carotenes, phenolic compounds	Hertog et al. (1992), Clifford (1999), Khachik et al. (1995), Clinton (1998), Nguyen and Schwartz (1999)
2	Gooseberry (*Phyllanthus emblica*)	Ascorbic acid, tannoids (emblicanin A and B, punigluconin)	Vasudevan and Parle (2007)
3	Grape (*Vitis vinifera*)	Resveratrol, anthocyanins, and other phenolics, Flava-3-nols (i.e., catechins), ellagic acid, myricetin, quercetin, kaempferol, and trans-resveratrol	Cantos et al. (2002), Pastrana-Bonilla et al. (2003)
4	Berberry (*Berberis vulgaris*)	Isoquinoline alkaloid	Host'álková et al. (2013), Singh et al. (2015)
5	Strawberry (*Fragaria ananassa*)	Flavanoids like anthocyanins, flavanols, flavonols, and phenolic acids, such as hydroxybenzoic acid and hydroxycinnamic acid, ellagic acid, ellagic acid glycosides, and ellagitannins	Giampieri et al. (2012), Aaby et al. (2005)
6	Blackberry (*Rubus laciniatus*)	Vitamin C and vitamin K, polyphenols, flavonoids, anthocyanins, salicylic acid, ellagic acid, and fiber	Zia-Ul-Haq et al. (2014), Sellappan et al. (2002)
7	Raspberry (*Rubus idaeus*)	Anthocyanin pigments, ellagic acid (from ellagitannins, see, for instance, the polyphenol ellagitannin), quercetin, gallic acid, cyanidins, pelargonidins, catechins, kaempferol, and salicylic acid	International Berry Health Benefits Symposium

(continued)

(continued)

8	Apple (*Malus domestica*)	Flava-3-nols (e.g., catechin, procyanidins), hydroxycinnamates (e.g., chlorogenic acid, caffeic acid, coumaroylquinic acid), flavonols (e.g., quercetin conjugates, dihydrochalcones, anthocyanins)	Kahle et al. (2005), Gerhauser (2008), Vrhovsek et al. (2004)
9	Goji berry (*Lycium barbarum*)	Ascorbic acid, beta-carotene, polysaccharides, lutein, zeaxanthin, B and E vitamins, minerals	Teng et al. (2013)

Tomato

The oral supplements of tomato seed aqueous extract significantly reduce rotenone-induced oxidative impairments and damage to the dopamine system. It is likely that acetylcholinesterase inhibition by seed extract may play a significant protective role in inhibiting rotenone-mediated apoptosis resulting in protection of dopaminergic neurons from demise in this model (Gokul and Muralidhara 2014).

Tomatine, a known steroidal glycoalkaloid, was extracted from the Chinese tomato *Solanum cathayanum*. The pretreatment with tomatine inhibits the release of cellular lactate dehydrogenase and increases SOD, CAT, and GPx activity and GSH content; it also reverses the downregulated protein expression of the brain derived neurotrophic factor (BDNF) and inhibits expression of Bax and activations of caspase-3 and caspase-9 in hydrogen peroxide-induced SH-SY5Y (human neuroblastoma) cells (Huang et al 2014).

Lycopersicon esculentum Mill. (tomatine and tomatidine) and the extracts from tomato leaves showed AChE and BChE inhibition capacity. Additionally, compounds/extracts revealed neuroprotective effects on glutamate-induced toxicity in SH-SY5Y neuroblastoma cells, without gastrointestinal toxicity, by preserving the mitochondrial membrane potential and reducing oxidative species (Taveira et al. 2014).

Di Matteo et al. (2009) proved that that repeated intake of a transgenic tomato fruit rich in beta-carotene will increase striatal dopamine and 3,4-dihydroxyphenylacetic acid levels and that the tomato-enriched diet exerted a positive effect against 6-hydroxydopamine-induced nigrostriatal lesions (Parkinson's disease) in rats. The beneficial effect of tomato is most likely due to the great lycopene content of the RS-enriched diet.

Tomato contains various agents that attenuate the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurodegenerative disease in mice (Suganuma et al. 2002).

Gooseberry

The anwala (amla) churna proved to reduce the brain cholinesterase activity and total cholesterol levels in a study conducted by Vasudevan and Parle (2007). Anwala churna may be confirmed as a useful remedy for the management of Alzheimer's

disease on account of its multifarious beneficial effects such as memory-improving property, cholesterol-lowering property, and anticholinesterase activity (Dasaroju and Gottumukkala 2014).

The tannoids of *Emblica officinalis* exert a protective effect against neuroleptic-induced tardive dyskinesia that is likely to be due to its earlier reported antioxidant effects in rat brain areas, together with the striatum (Bhattachary et al. 2000). The aqueous extract of *E. officinalis* showed antidepressant-like activity probably by inhibiting monoamine oxidase A and gamma-aminobutyric acid, along with its antioxidant property (Dhingra et al. 2012).

The solvent extracts of *E. officinalis* completely eliminated the generalized tonic seizures and also improved the retention latency in the passive avoidance task. In a dose-dependent manner, it also ameliorated the oxidative stress induced by pentylenetetrazol. These findings suggest the potential of hydroalcoholic extract of amla to be used as an adjuvant for treatment with antiepileptic drugs (Golechha et al. 2010).

Amla churna produced a dose-dependent improvement in memory of young and aged rats. It reversed the amnesia induced by scopolamine and diazepam. It may prove to be a useful remedy for the management of Alzheimer's disease due to its multifarious beneficial effects such as memory improvement and reversal of memory deficits (Vasudevan and Parle 2007).

Grapes

Grapes are one of the oldest cultivated plants. They are classified as true berries because the fruit wall or pericarp is fleshy all the way through. As results obtained from the study conducted by Balu et al. (2006), administration of grape seed extract for 30 days significantly reduced the level of DNA-protein cross-links in aged rats when compared to aged control rats. They revealed that grape seed extract has an inhibiting effect on the accumulation of age-related oxidative DNA damages in the spinal cord and in various brain regions such as the cerebral cortex, striatum, and hippocampus.

Grape seed extract attenuated the formation of oxygen free radicals, as measured by 8-isoprostaglandin F2 alpha and thiobarbituric acid-reacting substances in the hypoxic ischemic rat pup model. Grape seed extract improved the histopathologic brain score in the cortex, hippocampus, and thalamus (Feng et al. 2005).

Grape, which is easily available as juice form in the market, contains many flavonoids, polyphenols, and proanthocyanidins with antioxidant properties (Bagchi et al. 2000). Moreover, it has been reported that resveratrol, a polyphenolic antioxidant, is present in red wine and an active component in terms of the neuroprotective effect during cerebral ischemic injury (Huang et al. 2001; Wang et al. 2002).

GSE protected the delayed neuronal death of CA1 pyramidal cells by inhibiting oxidative DNA damage following transient forebrain ischemia (Hwang et al. 2004).

Rodrigues et al. (2012) demonstrated that both organic and conventional grape juices show important neuroprotective effects against pentylenetetrazol-induced oxidative damage in rats. This effect could be important in reducing neuronal

damage and, therefore, allow for a better quality of life for epileptic patients. Both juice types were able to protect from lipid and protein oxidative damage, decrease nitric oxide content, and increase enzymatic (superoxide dismutase and catalase) and nonenzymatic (sulfhydryl protein) antioxidant defenses in brain tissues.

Berberry

Berberine is an isoquinoline alkaloid that is found in some plants principally *Berberis*. It has some beneficial effect on anxiety, nociception, inflammation, psychosis, depression, and amnesia (Imanshahidi and Hosseinzadeh 2008; Kulkarni and Dhir 2008, 2010).

Mojarad and Roghani (2014) reported that berberine reduces NMDA receptor binding and inhibits NMDA receptor channel current in the brain. In addition, berberine protects neuronal cells from brain ischemia such as NMDA receptor antagonists (Cui et al. 2009).

Yoo et al. (2006) observed that the extract of berberine has protective effects against ischemic damage after ischemia/reperfusion. They investigated the chronological changes of NR1 and NR2A/B immunoreactivity in the hippocampal CA1 region early time after ischemia/reperfusion. Berberine pretreatment could attenuate spontaneous recurrent seizures. Since administration of berberine has decreased lipid peroxidation in kainite rats, it seems that the berberine favorable effect is due to its effectiveness in lessening of oxidative stress in rat. Their study indicates that berberine extract confers neuroprotection against transient ischemic brain injury through a mechanism that involves the reduction of NR1 expression.

Berberine has been shown to protect against ischemic brain injury by decreasing intracellular reactive oxygen species levels and subsequently inhibiting the mitochondrial apoptotic pathway (Zhou et al. 2008). Berberine also prevents changes in oxidative stress and choline esterase activity and consequently can improve the memory impairment seen in streptozotocin-induced diabetic rats (Bhutada et al. 2011).

In a study by Kim et al. (2014), ischemia showed increased glial fibrillary acidic protein (GFAP) and CD11b expression in the hippocampal CA1 region. On oral administration of berberine extracts, they observed suppression in ischemia-induced increments of GFAP and CD11b expression, showing that berberine can attenuate ischemic injury by inhibiting reactive astrogliosis and microglia activation.

Strawberry

A neurodegeneration cell model was used to evaluate the neuroprotective effect of the strawberry tree phenolics. The total phenolic content was estimated to be at 16.46 ± 3.66 (mg GAE g^{-1} dew). The neuroblastoma cell line SK-N-MC was subjected to an oxidative stress after preincubation with the fruit extracts (Fortalezas et al. 2010).

Heo and Lee (2005) performed the cell viability test using the 3-(4,5-dimethylth iazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay which showed that strawberry phenolics significantly reduced oxidative stress-induced neurotoxicity, because oxidative stress is also known to increase neuronal cell membrane breakdown. The protective effects appeared to be due to the higher phenolic contents, including anthocyanins as a major part.

Blackberry

Tavares et al. (2012) assessed the efficacy of blackberry polyphenolics and metabolites in a neurodegeneration cell model before and after simulated gastrointestinal digestion. It enhanced GSH levels and reduced ROS production. The digested polyphenol metabolites were able to maintain cell membrane integrity, protecting neurons from death.

The wild blackberries, *Rubus brigantinus* and *Rubus vagabundus*, presented neuroprotective effects in a study conducted by Tavares et al. (2013). Digested metabolites from these blackberries, at levels that could be found in human plasma, activated adaptive cellular stress response pathways such as caspase activation, GSH modulation, and also ROS diminishment. These effects protected neuronal cells against oxidative injury, one of the most important features of neurodegeneration.

Raspberry

Rubus coreanus, called as Korean black raspberry, belongs to the species of raspberry. The anthocyanins alleviated intracellular oxidative stress, as assayed by in vitro fluorescent measurements. The anthocyanins of *Rubus coreanus* showed neuroprotective effects on PC-12 cells in vitro against oxidative stress in a dose-dependent manner. Triple quadrupole LC/MS and Q-TOF LC/MS analyses revealed four major anthocyanins: cyanidin-3-*O*-sambubioside, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-xylosylrutinoside, and cyanidin-3-*O*-rutinoside. The protective effect on neuronal cells in vitro may be associated with their considerable antioxidant capacity.

Wang et al. (2012) studied the neuroprotective effects and mechanisms of action of total saponins from *Rubus parvifolius* L. (TSRP) on focal cerebral ischemia and reperfusion injury in rats. The ratio of Bax to Bcl-2 increased during hypoxia-induced neuronal death, which supports the hypothesis that the balance in protein expression of these two crucial factors determines cell survival or death following an apoptotic stimulus. Total saponin extract of *Rubus parvifolius* L. protects against ischemia/reperfusion injury. It reduces the cerebral infarct volume; and it may do so by increasing Bcl-2 expression and decreasing Bax expression, consequently inhibiting apoptosis.

Apples

Apple skin contains approximately 46 % of the total phenolics (McGhie et al. 2005), and specific flavonoids such as quercetin glycosides and cyanidin-3-*O*-galactoside are not found in the flesh of apples. From the study carried out by Keddy et al. (2012), it was proved that a flavonoid-rich fraction A4F isolated from Spy apples tends to posses maximum neuroprotective effect. Oral dosing of minimum 25 mg/kg, once daily for 3 days, reduced neuronal cell loss in the dorsal hippocampus and striatum of mice subjected to a model of HI-induced brain damage. It even shows synergistic actions between different phenolic compounds in this fraction that interact with functionally distinct targets.

One of the standardized model of neurodegeneration in which aged mice exhibit impaired cognitive performance and increased oxidative parameters in the brain tissue when subjected to a prooxidant diet (deficient in vitamin E and folate). However, when these mice received apple juice concentrate diluted in drinking water (0.5 %) for 1 month, there was a significant improvement in cognitive-related performance and reduced prooxidative status compared to controls (Tchantchou et al. 2005).

Apple juice concentrate prevents the characteristic decline in acetylcholine associated with aging and oxidative stress (Chan et al. 2006). Because cholinergic depletion is associated with impaired memory and reduced cognitive performance and acetylcholine reduction, in particular, is associated with Alzheimer's disease, there is potential importance in the ability of apple juice to maintain levels of this neurotransmitter.

Apple juice concentrate may work by other mechanisms, including the ability to suppress overexpression of presenilin-1, which is linked to the production of amyloid b peptide, a hallmark of Alzheimer's disease (Chan and Shea 2006, 2009). Apple juice also attenuated the neurotoxicity of amyloid beta peptide in vitro (Chan and Shea 2007). They propose that the content of *S*-adenosylmethionine in apple juice concentrate might account in part for these effects, because comparable effects were observed with *S*-adenosylmethionine alone.

Goji Berry

Promising research on the goji berry (*Lycium barbarum*) has shown a positive correlation between consumption of the fruit and neuroprotective benefits that minimize the ravaging effects of Alzheimer's (Teng et al. 2013). A staple in traditional Chinese medicine (TCM), goji, is an exceptional superfood that safeguards the health of both body and mind.

Goji berry is packed with nutrients like ascorbic acid, beta-carotene, polysaccharides, lutein, zeaxanthin, and B and E vitamins along with trace minerals such as zinc, copper, calcium, and selenium.

A study at the University of Hong Kong found aqueous extracts of goji disrupt the neurotoxic qualities of proteins within the brain which are associated with

Alzheimer's disease. Preliminary research has discovered that goji berry guards against the formation of specific compounds typically found in the brains of Alzheimer's patients. Using a laboratory model of Alzheimer's, scientists found that goji protected brain cells from the harmful effects of amyloid beta peptides, damaging agents that are linked to the pathological changes seen in the brains of Alzheimer's patients. These findings suggest that goji just might help prevent this memory-robbing disease. They showed treatment with 600 μg/ml goji berry effectively suppressed the activation of microglia. Microglia defend the brain by destroying invading pathogens in the innate immune response of the CNS (Kreutzberg 1996).

The researchers believe goji berry extract may play a pivotal role in creating future treatments for Alzheimer's.

Conclusion

The neuroprotective actions of dietary foods involve a number of effects within the brain, including a potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning, and cognitive function. This multiplicity of effects appears to be underpinned by two common processes. Firstly, they interact with important neuronal signaling cascades in the brain, leading to an inhibition of apoptosis triggered by neurotoxic species and to a promotion of neuronal survival and differentiation. These include selective actions on a number of protein kinase and lipid kinase signaling cascades, most notably the PI3 K/Akt and MAP kinase pathways which regulate pro-survival transcription factors and gene expression. It appears that the concentrations of flavonoids and phenolics encountered in the brain may be sufficiently high to exert such pharmacological activity of receptors, kinases, and transcription factors. Secondly, they are known to induce beneficial effects on the peripheral and cerebral vascular system, which lead to changes in cerebrovascular blood flow. These changes are likely to induce angiogenesis, new nerve cell growth in the hippocampus, and changes in neuronal morphology, all processes known to be important in maintaining optimal neuronal function and neurocognitive performance. The consumption of flavonoid-rich foods, such as berries and cocoa, throughout life holds a potential to limit neurodegeneration and prevent or reverse age-dependent deteriorations cognitive performances.

Berries are a natural source of food that helps to treat various diseases. On regular berry diet, many studies have been proven to show rich antioxidant property and improve the body regulation. A diet fortified with either blueberry or strawberry extract prevented the radiation-induced damage to the brain. Interestingly, strawberries had the most impact on spatial placement, whereas blueberries had the most impact on learning—indicating that various different berries may have different benefits to various brain regions in terms of protection. Numerous natural antioxidant/anti-inflammatory compounds found in plant food matrices, like fruits, especially berries (such as strawberry, blueberry, black currant, blackberry, blueberry, and mulberry), can offer neuroprotective effects (Essa et al. 2012).

Compliance with Ethics Requirements The authors declare that they have no conflicts of interest.

References

Aaby K, Skrede G, Wrolstad RE. Phenolic composition and antioxidant activities in flesh and achenes of strawberries (Fragaria ananassa). J Agric Food Chem. 2005;53(10):4032–40.

Abas F, Alkan T, Goren B, Taskapilioglu O, Sarandol E, Tolunay S. Neuroprotective effects of post conditioning on lipid peroxidation and apoptosis after focal cerebral ischemia/ reperfusion injury in rats. Turk Neurosurg. 2010;20(1):1–8.

Andersen JK. Oxidative stress in neurodegeneration: cause or consequence? Nat Med. 2004;10(1):S18–25.

Journal of Agricultural and Food Chemistry Presents Research from the 2007 International Berry Health Benefits Symposium. J Agric Food Chem ACS Publications, February 2008.

Arts ICW, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr. 2005;81:317–25.

Bagchi D, Bagchi M, Stohs SJ, Das DK, Ray SD, Kuszynski CA, Joshi SS, Pruess HG. Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. Toxicology. 2000;148:187–97.

Balu M, Sangeetha P, Murali G, Panneerselvam C. Modulatory role of grape seed extract on age-related oxidative DNA damage in central nervous system of rats. Brain Res Bull. 2006;68:469–73.

Battino M, Beekwilder J, Denoyes-Rothan B, Laimer M, McDougall GJ, Mezzetti B. Bioactive compounds in berries relevant to human health. Nutr Rev. 2009;67 Suppl 1:S145–50.

Bhandari PR, Kamdod MA. *Emblica officinalis* (Amla): a review of potential therapeutic applications. Int J Green Pharm. 2012;6:257–69.

Bhattachary SK, Bhattacharya D, Muruganandam AV. Effect of Emblica officinalis tannoids on a rat model of tardive dyskinesia. Indian J Exp Biol. 2000;38:945–7.

Bhutada P, Mundhada Y, Bansod K, Tawari S, Patil S, Dixit P, et al. Protection of cholinergic and antioxidant system contributes to the effect of berberine ameliorating memory dysfunction in rat model of streptozotocin-induced diabetes. Behav Brain Res. 2011;220:30–41.

Cantos E, Espín JC, Tomás-Barberán FA. Varietal differences among the polyphenol profiles of seven table grape cultivars studied by LC-DAD-MS-MS. J Agric Food Chem. 2002;50(20):5691–6.

Chan PH. Reactive oxygen radicals in signaling and damage in the ischemic brain. J Cereb Blood Flow Metab. 2001;21(1):2–14.

Chan A, Shea T. Supplementation with apple juice attenuates presenilin-1 overexpression during dietary and genetically-induced oxidative stress. J Alzheimers Dis. 2006;10:353–8.

Chan A, Shea T. Folate deprivation increases presenilin expression, gamma-secretase activity and A-beta levels in murine brain: potentiation by ApoE deficiency and alleviation by dietary S-adenosyl methionine. J Neurochem. 2007;102:753–60.

Chan A, Shea T. Dietary supplementation with apple juice decreases endogenous amyloid-beta levels in murine brain. J Alzheimers Dis. 2009;16:167–71.

Chan A, Graves V, Shea T. Apple juice concentrate maintains acetylcholine levels following dietary compromise. J Alzheimers Dis. 2006;9:287–91.

Clifford M. Chlorogenic acid and other cinnamates—nature occurrence and dietary burden. J Sci Food Agric. 1999;79:362–72.

Clinton SK. Lycopene: chemistry, biology and Implications for human health and diseases. Nutr Rev. 1998;56:35–51.

Cui H, Matsumoto K, Murakami Y, Hori H, Zhao Q, Obi R. Berberine exerts neuroprotective actions against in vitro ischemia-induced neuronal cell damage in organotypic hippocampal slice cultures: involvement of b cell lymphoma 2 phosphorylation suppression. Biol Pharm Bull. 2009;32:79–85.

Dasaroju S, Gottumukkala KM. Current trends in the research of *Emblica officinalis* (Amla): a pharmacological perspective. Int J Pharm Sci Rev Res. 2014;24(2):150–9.

Dhingra D, Joshi P, Gupta A, Chhillar R. Possible involvement of monoaminergic neurotransmission in antidepressant like activity of *Emblica officinalis* fruits in mice. CNS Neurosci Ther. 2012;18:419–25.

di Matteo V, Pierucci M, Di Giovanni G, Dragani LK, Murzilli S, Poggi A, Esposito E. Intake of tomato enriched diet protects from 6-hydroxydopamine-induced degeneration of rat nigral dopaminergic neurons. J Neural Trans Suppl. 2009;73:333–41.

Essa MM, Vijayan RK, Castellano-Gonzalez G, Memon MA, Braidy N, Guillemin GJ. Neuroprotective effect of natural products against Alzheimer's disease. Neurochem Res. 2012;37(9):1829–42.

Fasano A, Lozano AM. Deep brain stimulation for movement disorders: 2015 and beyond. Curr Opin Neurol. 2015;28(4):423–36.

Feng Y, Liu Y-M, Fratkins JD, LeBlan MH. Grape seed extract suppresses lipid peroxidation and reduces hypoxic ischemic brain injury in neonatal rats. Brain Res Bull. 2005;66:120–7.

Fortalezas S, Tavares L, Pimpão R, Tyagi M, Pontes V, Alves PM, McDougall G, Stewart D, Ferreira RB, Santos CN. Antioxidant properties and neuroprotective capacity of strawberry tree fruit (*Arbutus unedo*). Nutrients. 2010;2:214–29.

Gerhauser C. Cancer chemopreventive potential of apples, apple juice, and apple components. Planta Med. 2008;74(13):1608–24.

Giampieri F, Tulipani S, Alvarez-Suarez JM, Quiles JL, Mezzetti B, Battino M. The strawberry: composition, nutritional quality, and impact on human health. Nutrition. 2012;28(1):9–19.

Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. J Natl Cancer Inst. 1999;91:317–31.

Gokul K, Muralidhara. Oral supplements of aqueous extract of tomato seeds alleviate motor abnormality. Oxidative impairments and neurotoxicity induced by rotenone in mice: relevance to Parkinson's disease. Neurochem Res Aging Neurobiol Aging. 2014;1:128–32.

Golechha M, Bhatia J, Arya DS. Hydroalcoholic extract of *Emblica officinalis* Gaertn. affords protection against PTZ-induced seizures, oxidative stress and cognitive impairment in rats. Indian J Exp Biol. 2010;48:474–8.

Grosset KA, Grosset DG. Prescribed drugs and neurological complications. J Neurol Neurosurg Psychiatry. 2004;75:iii2–8.

Heo HJ, Lee CY. Strawberry and its anthocyanins reduce oxidative stress-induced apoptosis in PC12 cells. J Agric Food Chem. 2005;53:1984–9.

Hertog MGL, Hollman PCH, Katan MB. Content of potentially anticarcinogenic flavonols of 28 vegetables and 9 fruits commonly consumed in the Netherlands. J Agric Food Chem. 1992;40:2379–83.

Host'álková A, Novák Z, Pour M, Jirosová A, Opletal L, Kunes J, Cahliková L. Berbanine: a new isoquinoline-isoquinolone alkaloid from Berberis vulgaris (Berberidaceae). Nat Prod Commun. 2013;8(4):441–2.

Huang SS, Tsai MC, Chih CL, Hung LM, Tsai SK. Resveratrol reduction of infarct size in Long–Evans rats subjected to focal cerebral ischemia. Life Sci. 2001;69:1057–65.

Huang S-l, He H-b, Zou K, Bai C-h, Xue Y-h, Wang J-z, Chen J-f. Protective effect of tomatine against hydrogen peroxide-induced neurotoxicity in neuroblastoma (SH-SY5Y) cells. J Pharm Pharmacol. 2014;66:844–54.

Hwanga IK, Yoo KY, Kim DS, Jeong YK, Kim JD, Shin HK, Lim SS, Yoo ID, Kanga TC, Kim DW, Moon WK, Won MH. Neuroprotective effects of grape seed extract on neuronal injury by inhibiting DNA damage in the gerbil hippocampus after transient forebrain ischemia. Life Sci. 2004;75:1989–2001.

Iadecola C, Zhang F, Casey R, et al. Inducible nitric oxide synthase gene expression in vascular cells after transient focal cerebral ischemia. Stroke. 1996;27(8):1373–80.

Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. Phytother Res. 2008;22:999–1012.

Kahle K, Kraus M, Richling E. Polyphenol profiles of apple juices. Mol Nutr Food Res. 2005;49(8):797–806.

Keddy PG, Dunlop K, Warford J, Samson ML, Jones QR, Rupasinghe HP, Robertson GS. Neuroprotective and anti-inflammatory effects of the flavonoid-enriched fraction AF4 in a mouse model of hypoxic-ischemic brain injury. PLoS One. 2012;7(12):1–18.

Khachik F, Beecher GR, Smith JC. Lutein, lycopene and their oxidative metabolites in chemoprevention of cancer. J Cell Biochem. 1995;22:236–46.

Kim M, Shin MS, Lee JM, Cho HS, Kim CS, Kim YJ, Choi HR, Jeon JW. Inhibitory effects of isoquinoline alkaloid berberine on ischemia-induced apoptosis via activation of phosphoinositide 3-kinase/protein kinase B signaling pathway. Int Neurol J. 2014;18:115–25.

Kreutzberg GW. Microglia: a sensor for pathological events in the CNS. Trends Neurosci. 1996;19:312–8.

Kulkarni SK, Dhir A. On the mechanism of antidepressant-like action of berberine chloride. Eur J Pharmacol. 2008;589:163–72.

Kulkarni SK, Dhir A. Berberine: a plant alkaloid with therapeutic potential for central nervous system disorders. Phytother Res. 2010;24:317–24.

Lau FC, Shukitt Hale B, Joseph JA. The beneficial effects of fruit polyphenols on brain. Sci Nutr. 2005;43:1–18.

Lindvall O, Kokaia Z. Progress stem cells for the treatment of neurological disorders. Nature. 2006;441:1094–6.

McGhie TK, Hunt M, Barnett LE. Cultivar and growing region determine the antioxidant polyphenolic concentration and composition of apples grown in New Zealand. J Agric Food Chem. 2005;53:3065–70.

Mojarad TB, Roghani M. The anticonvulsant and antioxidant effects of berberine in kainate-induced temporal lobe epilepsy in rats. Basic Clin Neurosci. 2014;5(2):124–30.

Nguyen ML, Schwartz SJ. Lycopene: chemical and biological properties. Food Technol. 1999;53:38–53.

Pastrana-Bonilla E, Akoh CC, Sellappan S, Krewer G. Phenolic content and antioxidant capacity of Muscadine grapes. J Agric Food Chem. 2003;51(18):5497–503.

Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. Eur J Pharmacol. 2006;545(1):51–64.

Rodrigues AD, Scheffel TB, Scola G, Santos MT, Fank B, Vieira de Freitas SC, Dani C, Vanderlinde R, Henriques JAP, Coitinho AS, Salvador M. Neuroprotective and anticonvulsant effects of organic and conventional purple grape juices on seizures in Wistar rats induced by pentylenetetrazole. Neurochem Int. 2012;60:799–805.

Sellappan S, Akoh CC, Krewer G. Phenolic compounds and antioxidant capacity of Georgia-grown blueberries and blackberries. J Agric Food Chem. 2002;50(8):2432–8.

Singh A, Bajpai V, Kumar S, Arya KR, Sharma KR, Kumar B. Quantitative determination of isoquinoline alkaloids and chlorogenic acid in Berberis species using ultra high performance liquid chromatography with hybrid triple quadrupole linear ion trap mass spectrometry. J Sep Sci. 2015;38(12):2007–13.

Smith MA, Rottkamp CA, Nunomura A, Raina AK, Perry G. Oxidative stress in Alzheimer's disease. Biochim. Biophys. Acta. 2000;1502:139–44.

Sohal RS, Agarwal S, Sohal BH. Oxidative stress and aging in the Mongolian gerbil (*Meriones unguiculatus*). Mech Ageing Dev. 1995;81:15–25.

Suganuma H, Hirano T, Arimoto T, Inakuma T. Effect of tomato intake on striatal monoamine level in a mouse model of experimental Parkinson's disease. J Nutr Sci Vitaminol. 2002;48:251–4.

Sugawara T, Fujimura M, Noshita N, Kim GW, Saito A, Hayashi T, Narasimhan P, Carolina M. M, Pak HC. Neuronal death/survival signaling pathways in cerebral ischemia. NeuroRx. 2014;1(1):17–25.

Szulwach KE, et al. 5-hmC-mediated epigenetic dynamics during postnatal neurodevelopment and aging. Nat Neurosci. 2011;14:1607–16.

Tarazi FI, Sahli ZT, Wolny M, Mousa SA. Emerging therapies for Parkinson's disease: from bench to bedside. Pharmacol Ther. 2014;144(2):123–33.

Tavares L, Figueira I, McDougall GJ, Vieira HLA, Stewart D, Alves PM, Ferreira RB, Santos CN. Neuroprotective effect of blackberry (Rubus sp.) polyphenols is potentiated after simulated gastrointestinal digestion. Food Chem. 2012;131:1443–52.

Tavares L, Figueira I, McDougall GJ, Vieira HLA, Stewart D, Alves PM, Ferreira RB, Santos CN. Neuroprotective effects of digested polyphenols from wild blackberry species. Eur J Nutr. 2013;52:225–36.

Taveira M, Sousa C, Valentão P, Ferreres F, Teixeira JP, Andrade PB. Neuroprotective effect of steroidal alkaloids on glutamate-induced toxicity by preserving mitochondrial membrane potential and reducing oxidative stress. J Steroid Biochem Mol Biol. 2014;140:106–15.

Tchantchou F, Chan A, Kifle L, Ortiz D, Shea T. Apple juice concentrate prevents oxidative damage and impaired maze performance in aged mice. J Alzheimers Dis. 2005;8:283–7.

Teng P, Li Y, Cheng W, Liang Z, Shen Y, Wang Y. Neuroprotective effects of Lycium barbarum polysaccharides in lipopolysaccharide-induced BV2 microglial cells. Mol Med Rep. 2013;7:1977–81.

Vasudevan M, Parle M. Memory enhancing activity of Anwala churna (*Emblica officinalis Gaertn.*): an ayurvedic preparation. Physiol Behav. 2007;91(1):46–54.

Verstappen CC, Heimans JJ, Hoekman K, et al. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs. 2003;63:1549–63.

Vrhovsek U, Rigo A, Tonon D, Mattivi F. Quantitation of polyphenols in different apple varieties. J Agric Food Chem. 2004;52(21):6532–8.

Wang Q, Xu J, Rottinghaus GE, Simonyi A, Lubahn D, Sun GY, Sun AY. Resveratrol protects against global cerebral ischemic injury in gerbils. Brain Res. 2002;958:439–47.

Wang J, Zhang F, Tang L, Sun L, Song X, Cao L, Qiu Z, Zhou C. Neuroprotective effects of total saponins from *Rubus parvifolius* L. on cerebral ischemia/reperfusion injury in rats. Neural Regen Res. 2012;7(3):176–81.

White BC, Sullivan JM, DeGracia DJ, et al. Brain ischemia and reperfusion: molecular mechanism sofneuronal injury. J Neurol Sci. 2000;179:1–33.

WHO 2014, http://www.who.int/features/qa/55/en/.

Willcox JK, Catignani GL, Lazarus S. Tomatoes and cardiovascular health. Crit Rev Food Sci Nutr. 2003;43(1):1–18.

Yoo KY, Hwang IK, Lim BO, Kang TC, Kim DW, Kim SM, et al. Berberry extract reduces neuronal damage and N-Methyl-D-aspartate receptor 1 immunoreactivity in the gerbil hippocampus after transient forebrain ischemia. Biol Pharm Bull. 2006;29:623–8.

Zhou XQ, Zeng XN, Kong H, Sun XL. Neuroprotective effects of berberine on stroke models *in vitro* and *in vivo*. Neurosci Lett. 2008;447:31–6.

Zia-Ul-Haq M, Riaz M, Feo VD, Jaafar HZE, Moga M. *Rubus Fruticosus* L.: constituents, biological activities and health related uses. Molecules. 2014;19:10998–1029.