Insights of the pathophysiology of neurodegenerative diseases and the role of phytochemical compounds in its management

Zurina Hassan 1* and Raghava N. Sriramaneni 2

1 Centre for Drug Research, Universiti Sains Malaysia, 11800 Penang, Malaysia.
2 Department of Human Oncology, University of Wisconsin, Wisconsin, USA.
* Correspondence: zurina_hassan@usm.my; Tel.: +6017-5500804

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A neurodegenerative disease (ND) is defined as an irreversible disorder in most cases, leading to progressive loss of neurons and intellectual abilities. ND can lead to fatality in most circumstances, and the elderly above the age of sixty-five (65) constitute the major risk category. The most common type of ND includes Alzheimer’s disease (AD), and Parkinson’s disease (PD). Other NDs are Huntington’s disease (HD), motor neuron disease (MND), spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), and prion disease. ND strikes mainly in the middle to late life incidence expected to rise as the population ages. According to Harvard NeuroDiscovery Center, by the year 2030, 1 in every 5 Americans over the age of 65, if left untreated, may cause more than 12 million Americans to suffer from ND (Harvard NeuroDiscovery Center, 2021). According to Center for Disease Control and Prevention (CDC), 1 in every 3 seniors with AD will die as a result of dementia or the COVID-19 pandemic (Alzheimer’s Association, 2021).

The hallmarks of ND are protein aggregation, mitochondrial dysfunction, neuronal loss via apoptosis or necrosis, lysosomal dysfunction, excitotoxicity and metabolic syndrome. Increasing evidence demonstrates that metabolic syndrome is interrelated with many NDs because it affects middle-aged or older adults (Yalcin & Yalcin, 2018). During neurodegeneration, an innate immune response acts as the first line of defence to protect the host against invading pathogens (Medzhitov, 2008). Immune resident cells in the brain, such as microglia, have a vital homeostatic function, including the phagocytosis of fragmented and dying cells (Salter & Stevens, 2017). However, activated microglia produce large amounts of free radicals and contribute significantly to inflammation in AD (Wolozin & Behl, 2000). This inflammatory activity is beneficial for a short period. However, during ageing and in chronic neurodegenerative disease, both the innate and peripheral immune systems are defective and fail to detect or respond to imbalances in homeostasis due to the accumulation of protein aggregates. Subsequently, prolonged neuroinflammation with higher levels of pro-inflammatory cytokines leads to harmful consequences in CNS.

It is critical to note that protein abnormalities that define ND can be presented before the onset of clinical features (Dugger & Dickson, 2017). In ND, abnormal protein conformations and cellular and neuroanatomical distribution constitute the major histopathologic features essential for disease state diagnosis (Kovacs, 2016). These proteins are considered NDs biomarkers. For instance, AD is characterised by the
extracellular deposition of Aβ fibrils, abnormally phosphorylated tau protein accumulation, neuritic senile plaques, and neurofibrillary tangles (Marks et al., 2017). In addition, prion diseases are a cellular form of prion protein (PrPc) and scrapie isoform of prion protein (PrPSc) (Mehrpour & Codogno, 2012) whereas α-synuclein protein (Dauer & Przedborski, 2003) and Lewy bodies (Licker et al., 2009) have key roles in the neuropathology of PD. In HD, unstable huntingtin (Htt) protein aggregates accumulate in neurones leading cell death (Roos, 2010). MND is contributed by glutamate excitotoxicity of neurones (Relja, 2004), whereas loss of motor neurons in the spinal cord is observed in SMA (Coovert et al., 1997). In SCA, aggregation of proteins with long polyglutamine tract (PolyQ) forming inclusions in the cytoplasm or nucleus of vulnerable neurones, contributing to the progression of the pathology such as neuronal dysfunctions and subsequent neurodegeneration (Pilotto & Saxena, 2018).

Many models and ideas have been used to identify the exact pathophysiology and mechanisms of ND. The most frequently discussed risk amongst the general population with ND is ageing. Human brain ageing can be investigated using aged non-human primates and some other higher-order animal species. However, it is challenging to monitor complete neuropathological or clinical phenotypes seen in humans in these models. Hence, cell models, animal models, and genetically engineered non-mammals (Caenorhabditis elegans, Drosophila melanogaster and zebrafish) are employed to recapitulate the specific disease mechanisms involved in ND, including the screening of therapeutic compounds. The genetically engineered mice have been the most popular and widely used animal model to study ND (Trancikova et al., 2011). The commonly used study model for AD research includes the transgenic animal model targeting amyloid-beta precursor protein (APP), presenilin, tau or the human apolipoprotein E gene (APOE) gene. For PD research, classic neurotoxin-induced animals are usually employed. Several compounds known to be toxic to dopaminergic neurones can be used to produce parkinsonism, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, rotenone and 6-hydroxydopamine. Animal models of HD include both toxin-induced models (mitochondrial toxin 3-nitropropionic acid or excitotoxins such as kainate, ibotenate, quinolinate), genetic models such as transgenic mice (R6/2, R6/1, N171-82Q, Yeast artificial chromosome expressing complete human htt protein) and knock-in mouse model (HdhQ92 mouse, HdhQ111 mouse, CAG140 mouse, CAG150 mouse) (Ramaswamy et al., 2007).

Unfortunately, several clinical trials targeting ND have raised doubts about the translatability of animal disease models to humans. To bridge the gap between animal and human studies, three-dimensional (3D) cell culture models have been developed from human or animal cells. Traditionally, two-dimensional (2D) cell culture was used in vitro, but its efficiency is questionable because the environment is far from mimicking the in vivo state. Hence, the 3D cell culture creates an artificial environment that allows the biological cells to grow and interact to mimic a living organ and its microarchitecture. There are several advantages of 3D model such as (1) allows better control of variables that are difficult to regulate in vivo; (2) reproducible cellular and molecular mechanism; (3) allows human-based models to be grown by using human cells for drug testing, disease modelling and diagnoses; (4) can overcome the graft limitations; (5) allows faster and affordable translational studies involving the identification of the mechanism of action together with any associated risks (Bedard et al., 2020; Slanzi et al., 2020).

Pathological changes of neurons and loss of synaptic protein are the key features in many ND, including dementia. The latter seems to be directly linked to cognitive deficits from the early stages of dementia and precede neuronal degeneration (Berecki et al., 2018; Kashyap et al., 2019; Sharifi-Rad et al., 2020a). As shown in Figure 1, synaptic loss was established from activated microglia, which engulf and excessively prune the synapses. In addition, the activated microglia also release pro-inflammatory cytokines, which can have direct excitotoxic effects on the synapses (Hong et al., 2016; Wang et al., 2015). Current therapeutic interventions focus on the treatment of neuronal loss or synaptopathy targeting at the theoretically distinct processes of maintenance, compensation, and recovery of synaptic function, which can significantly impact cognitive function (Sheng et al., 2012). Most of the new drug discoveries in an attempt to improve the efficiency of remaining synapses in brains were based on its pharmacological classes such as anti-cholinesterase (Anand & Singh, 2013), selective serotonin reuptake inhibitors (Chow et al., 2007) and N-methyl-D-aspartic acid (NMDA) antagonists (Prentice et al., 2015).

The most common physiological symptoms of ND are elevated oxidative/nitrosative stress, mitochondrial dysfunction, protein misfolding /aggregation, synapse loss, and decreased neuronal survival. This chronic neurodegenerative disorder leads to progressive dementia and deterioration of cognitive function.
Figure 1: Signalling pathway of neurodegenerative disease. Defective innate immune reactions associated with ageing contributes to neurodegenerative diseases. Brain resident microglia and astrocytes can cross-talk each other and help to form the protein aggregates and damages the neuronal network with the help of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and C-reactive protein. Alternatively, synaptic pruning and microglia can also agonise neuronal degradation independent of protein aggregation (Gan et al., 2018). Herbal active compounds listed in Table 1 can antagonise these signalling responses and protect against neuronal cell damage.

Current available drugs focus primarily on temporary symptomatic relief. Hence, there is a high demand for the discovery of novel therapies and neuroprotective agents to prevent and retard the progression of ND (Sharifi-Rad et al., 2020b). Recently, some convincing evidence has been published regarding the use of traditional herbs and phytochemicals to delay the onset and slow the progression of ND. Most of the traditional herbal medicines are prepared from crude materials, and there are concerns about their specific medicinal effects and reproducibility, mode of action and the active ingredients (Kim et al., 2010). Furthermore, these natural phytochemicals are less toxic than novel synthetic drugs. Hence, many active compounds have been isolated and identified from medicinal plant extracts (Ansari & Khodagholi, 2013). These include lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids, which have shown various beneficial pharmacological activities, such as anti-inflammatory, anti-amyloidogenic, anti-cholinesterase, anti-oxidant, inhibiting protein misfolding, reducing neuroinflammation, anti-apoptotic, neurotrophic, acetylcholinesterase (ACHE) inhibition, monoamine oxidase (MAO) inhibition and anti-thrombotic (Howes et al., 2003; Sharifi-Rad et al., 2020b).

Neurotrophins play a vital role in the survival, maintenance and regeneration of specific neuronal populations in the brain (Baazaoui & Iqbal, 2018). Examples of these neurotrophins are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5. Neurotrophins depletion accelerates the progression of ND, and therefore, replacing such neurotrophins is potentially therapeutic (Venkatesan et al., 2015). Phytochemicals from natural sources and synthetic derivatives have
| Name of the plant | Active constituents | Uses | References |
|-------------------|---------------------|------|------------|
| **Ginkgo** *Ginkgo biloba* | Terpene trilactones, ginkgolides A, B, C, J and bilobalide, biflavones, proanthocyanidins, alkylphenols, polyphenols | To treat moderate dementia and AD, improve memory, neuroprotection | Van Beek, 2002; Defeudis, 2002; Tchantchou et al., 2009; Yakoot et al., 2013 |
| **Rosemary** *Salvia rosmarinus* | Rosmarinic acid, carnosic acid, camphor, caffeic acid, ursolic acid, betulinic acid, rosmaridiphenol and rosmanol | Improves memory, prevents stroke, to treat AD, anti-oxidant, antibacterial, anti-inflammatory, anticancer, antiviral and neuroprotective effects | Moss et al., 2003; Peterson & Simmonds, 2003; Alkam et al., 2007; Kantar Gok et al., 2015 |
| **Turmeric** *Curcuma longa* | Curcumin | To treat AD, antineurodegeneration, reducing α-synuclein oligomerisation in PD | Funk et al., 2006; Mishra & Palanivelu, 2008; Aggarwal et al., 2006; Hamaguchi et al., 2010 |
| **Ginseng** *Panax ginseng* | Ginsenosides, or saponins, 20(S)-protopanaxadiol (PPD) and 20(S)-protopanaxatriol (PPT) | To treat neurological disorders such as PD, AD, and stroke | Tawab et al., 2003; Cho, 2012 |
| **Brahmi** *Bacopa monnieri* | Saponins, triterpenoids, alkaloids, sterols, betulinic acid, polyphenols and sulfhydryl | Nerve tonic, anti-diuretic, to treat rheumatism, epilepsy, insomnia, improves memory and treatment of AD | Gohil & Patel, 2010 |
| **Shankhpushpi** *Convolvulus pluricaulis* | triterpenoids, flavonol glycosides, anthocyanins, and steroids | Nootropic and memory-enhancing activity, anti-stress, treatment of anxiety, mental fatigue, and insomnia, treat AD | Sethiya et al., 2009; Malik et al., 2011 |
| **Gotu kola** *Centella asiatica* | Asiatic acid and asiaticoside | Improves memory, neuroprotection, anti-oxidant, AD and PD treatment | Defeudis, 2002; Chen et al., 2015; Dhanasekaran et al., 2009 |
| **Ginger** *Zingiber officinale* | gingerols, shagoals, bisabolene, zingiberene, and monoterpenes | Enhances cognitive functions in AD | Ali et al., 2008; Oboh et al., 2012 |
| **Garlic** *Allium sativum* | Allicin | Neuroprotection, improve memory, anti-oxidant, treatment of AD, ischemia | Essa et al., 2012; Borek, 2006; Nilbert et al., 2017 |
| **Citrus** *Citrus sinensis* | Quercetin | Anti-oxidant, anticancer, antiviral, anti-inflammatory, treat AD, reduce MAO | Ossola et al., 2009; Russo et al., 2012; Bischoff, 2008; Jiménez-Aliaga et al., 2011 |
| **Tea** *Camellia sinensis* | Epigallocatechin-3-gallate | Anti-oxidant, anticancer, treatment of ND and AD | Ahmad et al., 1997; Biasibetti et al., 2013; Lee et al., 2009 |
| **Chinese goldthread** *Coptis chinensis* | Berberine | Anti-oxidant, treat AD, improve memory, AChE inhibitor | Kulkarni & Dhir, 2010; Durairajan et al., 2012; Zhu & Qian, 2006; Huang et al., 2017 |
| **Grapevine** *Vitis vinifera* | Resveratrol | Anticancer, anti-inflammatory, anti-oxidant, can lower blood glucose levels, and neuroprotective effects, treat AD, Improve memory | Li et al., 2012; Kumar et al., 2007; Karrthick et al., 2016 |
| **Toothed firmoss** *Huperzia serrata* | Huperzine A | improve memory, AChE inhibitor, treat AD | Ha et al., 2011; Ratia et al., 2013; Wang et al., 2011; Rafii et al., 2011 |

**AD**: Alzheimer’s disease; **PD**: Parkinson disease; **MAO**: monoamine oxidase; **ND**: Neurodegenerative diseases; **AChE**: acetylcholinesterase
been shown to have potential in mediating neurotrophins. For instance, 3,7-dihydroxy-2,4,6-trimethoxy-phenanthrene, dionisopside B, lignan derivatives, ginkgolide B, 4,6-dimethoxyphenanthrene-2,3,7-triol, spicatoside A, ginsenoside Rg3, limonoid derivatives, quercetin, cyanidin-3-O-β-glucopyranoside, clerodane diterpenoids, apigenin derivatives, and quinic acid derivatives can prevent neurodegeneration by inducing neurotrophic factors and boosting anti-oxidant activity, and inhibit the production of ROS and inflammatory mediators (details of mechanism can be obtained from Venkatesan et al., 2015). Furthermore, neurotrophic factors and the Wnt pathway play a critical role in restoring synaptic loss and behavioural deficits (Eyjolfsdottir et al., 2016).

Phytochemical compounds with anti-oxidant and anti-inflammatory activities have the potential to treat ND. Good examples of these are flavonoids which possess high anti-oxidant properties. Flavonoids have low molecular weight, and they belong to polyphenolic anti-oxidants present in fruits, vegetables, and beverages such as wine and tea (Panche et al., 2016). In addition, these flavonoids can also be found in the roots and leaves of Andrographis paniculate (known as Hempedu bumi in Malay) (Subramaniam et al., 2015). Ficus deltoides consists of at least 25 different flavonoids with high anti-oxidant properties (Azemin et al., 2014; Hakiman & Maziah, 2009). Flavonoids and tannins derived from Uncaria gambir demonstrated anti-oxidant properties that prevent damage caused by free radical-mediated processes (Ningsih et al., 2014).

Anthocyanins have anti-inflammatory activity as they inhibit cyclooxygenase enzymes. These flavonoids inhibit the expression of vascular cell adhesion molecules (VCAM), thus inhibiting the reaction and adhesion of endothelial cells with leucocytes. These compounds are believed to decrease the levels of interferon necrotic factor-gamma, interleukin-2 and inhibition of mast cell degranulation (Joseph & Jini, 2011; Pataki et al., 2002). Ferulic acid, another phenolic acid, has a broad therapeutic effect against neurodegenerative and inflammatory diseases. It is attributed partly due to the anti-oxidant activity of this phenolic acid. The ferulic acid prevents lipid peroxidation and scavenges superoxide free ion radicals (Joshi et al., 2001). This phenolic acid reduces inflammatory mediators like tumour necrotic factor-alpha, prostaglandin E2 (Appendino et al., 2006), protects proteins, DNA and lipids from oxidative stress, thus exerting anticancer properties (Delmas et al., 2006).

Tannins which can be found in Eurycoma longifolia possess antibacterial (Danial et al., 2013), anti-inflammatory (Varghese et al., 2013), and anti-oxidant due to their high concentration of superoxide dismutase (Mohd Effendy et al., 2012). Tannins are also present in Piper bettle with anti-oxidant and anti-inflammatory activities (Abraham et al., 2012; Datta et al., 2011; Sripradha, 2014).

Terpenoids present in most plants like Andrographis paniculate, Panax ginseng, Gynura procumbens, Labisia pumila, Orthosiphon stamineus, Phyllanthus niruri. Terpenoids possess both anti-oxidant and anti-inflammatory activities. Ginsenosides (one of the terpenoids) from Panax ginseng has been shown to reduce Aβ levels by promoting Aβ degradation and enhancing nepriylsin gene expression, a rate-limiting enzyme in Aβ degradation (Yang et al., 2009). Ginkgolides, a cyclic diterpene isolated from Gingko biloba has been extensively studied for its neuroprotective effects (Shi et al., 2009). Cannabinoids are monoterpene derived from Cannabis sativa, inhibiting AChE-induced Aβ aggregation and reduce Aβ-induced toxicity (Eubanks et al., 2006). Oleanolic acid from Aralia cordata rescued neuronal death induced by Aβ in cultured rat cortical neurons and improves Aβ-induced memory deficit in mice (Cho et al., 2009). Another triterpene isolated from Polygala tenuifolia known as tenuifolin reduces Aβ secretion by inhibiting β-secretase, one of the enzymes responsible for cleaving APP to Aβ (Lv et al., 2009). Ursolic acid derived from Origanum majorana exhibits a neuroprotective effect against Aβ. Ursolic acid can effectively inhibit AChE activity and Aβ binding to microglia, reducing the production of pro-inflamatory cytokines and neurotoxic reactive oxygen species (Wilkinson et al., 2011). Table 1 summarises the selected potential herbal plants with the phytochemical components that show promise for NDs treatment.

Taken together, herbal medicines containing phytoactive compounds may show a great promise for the future treatment and management of NDs. Therefore, to effectively treat NDs, the natural active compounds need to be evaluated, standardised, explored and learned through pre-clinical research using various ND disease models. On the other hand, synthetic medications can temporarily relieve the symptoms and may not be the permanent solution to cure the NDs completely. Together with the help of clinicians and researchers, natural medicines can be made safer and more effective to treat ND patients. Finally, researchers need to explore biological
mechanisms involved in NDs and expand the knowledge of natural compounds by conducting the fundamental research critical to combat ageing-related NDs.

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