Flavonoids and Diarylheptanoids: Neuroprotective Activities of Phytochemicals

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Abstract. Plants are often used as sources of lead compounds with phenolic compounds frequently attributed to physiological effects. Flavonoids and diarylheptanoids are important groups of phenolic compounds that impart antioxidant, antitumorigenic, antiinflammatory, and neuroprotective effects. These neuroprotective effects can be harnessed to develop treatments for neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Recent discoveries have characterized new neuroprotective compounds and/or sources and tested treatments on cell lines and model animals to improve treatments for future persons with neurodegenerative disorders.

Introduction

The use of phytochemicals as a source of lead compounds in pharmaceutical drug discovery is well known [1, 2]. These phytochemicals are often extracts from plants used in traditional medicine and may be independent active ingredients or natural formulations that can be used to enhance the desired effects of drugs [3, 1]. The biological activity of plants may be due to phenolic compounds that are known to confer antioxidant, antitumorigenic, antiinflammatory, or other favourable activities [3-5]. One of the many potential pharmaceutical uses of phenolic compounds is the treatment and prevention of neural diseases [6-8]. Phenolic compounds that can cross the blood-brain barrier can indicate neuroprotective functions and clinical potential of the central nervous system which has a limited ability to repair and regenerate [3, 9, 10]. Two major groups of neuroprotective phytochemicals are diarylheptanoids, such as curcumin, and flavonoids, such as quercetin (Fig. 1) [6, 11]. Flavonoids and diarylheptanoids are neuroprotective, are able to protect neurons from damage, particularly through free radical scavenging activity, modulation of neuroplasticity resulting in an increase in cognitive, behavioral and/or emotional function, e.g., improving memory [11, 6, 12]. These compounds may serve as active ingredients for novel therapies in the treatment of neurodegenerative diseases including Alzheimer's and Parkinson's disease [6].

Figure 1. Structure of Curcumin (a) and Quercetin (b) [13-15].

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, ALS, and Huntington's disease, are characterized by memory loss, irregular movement or behaviour and emotional difficulties due to a loss of neurons in the central nervous system [1, 16]. Alzheimer's disease is a neurodegenerative disease in which beta-amyloid accumulates causing loss of memory which may result in dementia [11]. Parkinson's disease is a result of loss of dopaminergic receptor function, thereby reducing dopamine and causing symptoms, such as resting tremors and rigid limbs

[17]. These neurodegenerative disorders may be caused by a combination of environmental, genetic, and age-related factors and can be treated using conventional drug therapies which are currently only moderately effective and often focus on symptom control not reversal or prevention of progression [16, 8]. Oxidative stress is often a factor in neurodegenerative disease development and progression and can be remedied using antioxidant drugs, or natural compounds i.e., phenolic compounds including flavonoids and diarylheptanoids [3, 1, 18]. This paper will outline recent discoveries of flavonoids and diarylheptanoids for the treatment of neurodegenerative diseases.

Neurodegenerative Diseases

Quercetin and curcumin are two of the most well-known anti-inflammatory, antioxidant and consequently neuroprotective natural compounds [3]. Quercetin research shows potential for the treatment of Alzheimer's disease, as demonstrated in a mice model which administered quercetin intraperitoneally every 48 hours for 3 months resulted in decrease in beta-amyloidosis and tauopathy in the hippocampus and amygdala and an increase in cognitive performance although it may be toxic at high (greater than 100 μ M) concentrations [11, 19]. Curcumin has attracted a lot of attention due to its potential for both cancer and neurodegenerative disease treatment by reducing the damage due to oxidative stress in the body [20-22]. Research has shown that curcumin increases hippocampal neurogenesis in rats thereby preventing and potentially reversing cellular effects of neurodegenerative diseases [20-22]. From a pharmaceutical view one of the major hurdles with curcumin stems from its low solubility and low retention time in the body, these hurdles are being overcome by innovative delivery systems such as the PLGA nanoparticles which one group found increases half-time in the cerebral cortex and hippocampus by more than 1.5 fold [22]. Building upon the success of Quercetin and Curcumin for the treatment of neurodegenerative diseases, other flavonoids and diarylheptanoids have been studied for pharmaceutical potential.

Alzheimer's

Investigations into specific activity of these molecules on Alzheimer's disease models were conducted in order to assess disease-specific potential of compounds [1, 8, 23]. Nobiletin from citrus was tested at a 30mg/kg dose over three months in a triple transgenic mouse model and was found to reverse the short-term memory and recognition task performance by reducing reactive oxygen species in the hippocampus [1]. In humans a small group of Australian adults over age 65 with Alzheimer's related dementia showed an increase in cognitive functions when their diet had a higher total flavonoid content [24].

Parkinson's

The effect of flavonoids (flavonoid glycosides and quinochalones) from safflower extract increased PC12 cell viability and behavioral performance of 6-OHDA (Parkinson's model) rats [12]. The use of flavonoids, such as naringin, to suppress microglial activation in animal models of Parkinson's disease was tested and showed neuroprotective behaviour in the substantia nigrapars compacta in the rat brain. However, at high levels of inflammation the neuroprotective flavonoids generated neurotoxic compounds [17].

Neuroprotective Phytochemical Studies

The neuroprotective effects of flavonoids and diarylheptanoids were tested using H2O2 and glutamate stressed cell lines [18, 14, 25-31]. This test mimics oxidative stress that is attributed to the development of neurodegenerative disorders [18]. *Girsium setidens*, *Aster scaber*, *Passiflora actinia*, *Ginko Biloba*, *Acel nikoense*, *Alnus glutinosa*, *Alpinia officinavum* Hance, *Panax ginseng*, *Schisandra chinensis*, *Rehmannia glutinosa*, *Flammulina velutipes*, *Rhododendron fortune*, *Morus alba*, and *Carya cathayensis* Sarg. were all recently shown to contain flavonoids and/or diarylheptanoids that could counteract the neurodegenerative effects of oxidative stress [18, 25, 9, 13, 28-35]. The ability of flavonoids to cross the blood-brain barrier was enhanced by

alpha-tocopherol as verified by the increase in the presence of flavonoid derivatives in the brain and plasma as detected by high performance liquid chromatography mass spectrometry [14]. The use of rutin on rats in 100 mg/kg/day dosage for five weeks suggests an application for rutin in the treatment of the neurodegenerative eye disease diabetic retinopathy since rutin promotes nerve growth [36]. While flavonoids and diarylheptanoids were found to activate the PI3/Akt, MAPK, PKA, CHOP pathways and Nrf2 concentration, they did not affect Ca²⁺ homeostasis [28, 27, 37-39]. A potential application of neuroprotective flavonoids and diarylheptanoids is in the protection of the brain from damage caused by ischemic stroke as demonstrated by the ability of flavonoids to regulate blood pressure and serum lipid levels [26].

Conclusion

The search for cures to neurodegenerative diseases is well rooted in phytochemical analysis. The antioxidative role of flavonoids and diarylheptanoids plays an important role in the hunt for effective treatments and prevention of disease. In particular, research has focused on Alzheimer's disease and Parkinson's disease treatments by flavonoids and diarylheptanoids due to the deficiencies in current treatments. Diarylheptanoids and flavonoids provide new groups of compounds that can be used to develop novel classes of drug treatments for neurodegenerative diseases that target disease mechanisms. Further research into the pharmacokinetics and pharmacodynamics of phenolics may lead to the development of biologically available and highly bioactive drugs.

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