

Phytochemicals from mulberry extract (*Morus sp.*): Antioxidant and neuroprotective potentials

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ABSTRACT

ROS are involved in aging, progressive neuronal death, and age related disorders. During the last decade, there is increasing evidence indicating the beneficial role plant rich phytochemicals for the treatment of oxidative stress-induced disorders in the brain due to their antioxidant activity. Mulberry extract has been reported to have antioxidant activity which attenuates deleterious effects of oxidative stress. Their neuroprotective effects *in vitro* and *in vivo* models of neurodegenerative disorders have been documented. In this paper, mechanisms of action of polyphenols mulberry extracts and related compounds as neuroprotectors in brain damage and aging will be reviewed.

INTRODUCTION

Generally, phytochemicals and bioactive compounds derived from medicinal plants have the ability of preventing or curing some diseases. Neurodegenerative diseases are characterized by progressive nervous system dysfunction and affected central or peripheral structures of the nervous system. Oxidative stress may play a crucial role in neuronal death and physiopathology of neurodegenerative disorders. Among active phytochemicals are phenolic compounds, or polyphenols, products of the secondary metabolism constitute one of the most numerous and widely-distributed groups of substances in the plant. Polyphenols exhibit a wide range of biological effects as a consequence of their antioxidant properties. they are known to have the ability to scavenge a wide range of reactive species,

including hydroxyl radicals, peroxy radicals hypochlorous acid and superoxide radical, O₂.

Mulberry or *Morus* (L., Moraceae) is a genus of 10–16 species that are distributed Worldwide (Iqbal *et al.*, 2012). Mulberry is found from temperate to subtropical regions of the Northern hemisphere to the tropics of the Southern hemisphere and they can grow in a wide range of climatic, topographical and soil conditions.

Mulberry is known in some traditional and folk Chinese medicinal formulas and several studies indicating that it may provide certain health benefits. Mulberry extracts are rich in many phytochemicals and bioactive compounds leading to several pharmacological and biological properties. Apart from antibacterial, antiviral (Wang *et al.*, 2008), antitussive, hypoglycemic (Nickavar *et al.*, 2009; Naowaboot *et al.*, 2009), hypotensive (Chirino *et al.*, 2009), antiatherogenic, antihyperlipidemia (Nickavar *et al.*, 2009, Varposhti *et al.*, 2007), diuretic, astringent, antioxidant (Yang *et al.*, 2010, Kobayashi *et al.*, 2010) and α -amylase inhibitory effects (Nickavar *et al.*, 2009)

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In recent years, numerous data in the literature indicate that phytochemicals rich- mulberry extract related exhibit wide range of protective and therapeutics role in the pathogenesis of brain disease. This protective effect is most likely due to the presence of phenolic compounds in mulberry. Besides, numerous pharmacological activities of mulberries were correlated to phenolic qualitative and quantitative contents, particularly the flavonoids and anthocyanin they contain and a well correlation between antioxidant activity and phenolic constituent (Chen *et al.*, 2006). Various studies have illustrated that mulberry extracts may be a potential agent in neuroprotection and brain insults. Their neuroprotective activity has been documented. In this review we focus on neuroprotective abilities and mechanism of action of mulberry extract against neurodegenerative diseases. Mulberry extract and its related phenolic compounds have the ability to remedy the symptoms of degenerative diseases particularly Alzheimer's disease (AD) and Parkinson's disease (PD), and there to prevent age-related neurodegeneration. Mulberry extract exerts strong antioxidative and anti-inflammatory activities and also exhibits anti-convulsive, antidepressant, and improvement of memory deterioration in ageing and on the promotion of cognition in senescence-accelerated.

Phenolic phytochemicals in mulberry

Several phenolic compounds in mulberry leaves have been previously described (Onogi *et al.*, 1993; Matsuoka *et al.*, 1994; Katsube *et al.*, 2006). Among polyphenols the most present in mulberries are hydroxycinnamoyl esters, flavonol glycosides and some aglycone compounds. Hydroxycinnamates are the most important class of the phenolic acids present in mulberries. Caffeoylquinic acid and chlorogenic acid isomers are the most abundant cinnamic acid in the extract although quercetin and kaempferol are the most important present flavonols. Others flavonols glycosides, rutin, isoquercitrin, quercetin 3-glucoside, astragaloside and kaempferol glucoside have been reported in mulberry leaves (Onogi *et al.*, 1993; Matsuoka, Kimura, & Muraoka, 1994). Katsube *et al.* (2008) identified the presence of Kaempferol 3- malonylglucoside in ethanol extract of *Morus Alba* leaves. Some others additional phenolic compounds were detected in polyphenol-rich extract from Mulberry such as gallic acid, catechin and derivatives, protocatechuic acid gallo catechin gallate epicatechin and naringenin (Chan *et al.*, 2010). More recently, two new Quercetin isomers were identified in methanolic extract of *Morus alba* cultivar: Quercetin -3-O-glucoside-7-O-rhamnoside and Quercetin glycosylated with rhamnoside -glucoside, attached at the C-3 and C-7 positions (Thabti *et al.*, 2012). Several others functional phytochemicals, such as 1-deoxyojirimycin (DNJ), γ -aminobutyric acid (GABA) and 2-arylbenzofurans, have been isolated as major active components with biological activities from mulberry leaves (Doi *et al.*, 2001)

Antioxidant potential

Prior studies has been investigated the antioxidant activity of Mulberries extracts and it has been reported to have

potent antioxidant Activity (Zhang *et al.*, 2008). Generally, extracts from different parts of Tut plant parts: the stems, roots, bark, leaves, fruits, and seeds had strong hydroxyl and DPPH radical scavenging activities (Khan *et al.*, 2013). Further, it has been reported that mulberry leaf extract has antioxidant activity (Katsube *et al.*, 2009; Lim *et al.*, 2013). Since structural features of phenolic compounds are responsible for the antioxidant activity, the antioxidant activities of the tested mulberry leaves may be related to their total phenol content and the underlying mechanism suggested as explaining the neuroprotective effect of mulberries polyphenolic compounds can be principally summarized as scavenging intracellular ROS and inhibition of LDL oxidation. Doi, Kojima, and Fujimoto (2000) reported that 1-butanol extract of mulberry leaves scavenged the DPPH radical and inhibited the oxidative modification of rabbit and human LDL.

The dominant phenolic acid in mulberry extracts is chlorogenic acid and its isomers. Chlorogenic acid exhibited the largest contribution to DPPH radical scavenging activity, to the total amount of activities. Flavonoids are known to have antioxidant activities *in vitro*, being able to scavenge a wide range of reactive species, including hydroxyl radicals, peroxy radicals hypochlorous acid and superoxide radical, O₂ (Rice-Evans *et al.*, 2000). There are four main groups of flavonoids, including flavones, flavanones, catechins, and anthocyanins. Katsube (2009) reported that the most abundant flavonol glycoside was quercetin, the greatest contributor to antioxidant activity in mulberry leaves. In contrast, kaempferol glycosides as an aglycon exhibited only a slight contribution to DPPH radical scavenging activity due to their weak scavenging abilities and the presence of a 3', 4'-catechol moiety in the B ring correlated with high activity (Wang *et al.*, 2006). Therefore the 3',4'-catechol moiety of flavonol glycosides may affect antioxidant activity to a greater degree than those of their aglycons. Further, flavonoids chelate transition metal ions such as iron and copper, decreasing their ability to promote reactive species formation (Mira *et al.*, 2002)

Mulberry fruits have recently been received much attention as potential sources of anthocyanins and their biological effects on human health. Bae, S. H *et al.* (2007) confirms that extract of mulberry fruits represents a significant source of anthocyanic antioxidants. Therefore anthocyanins are considered as secondary metabolites with potential nutritional value and antioxidant capacity. The antioxidant activity of anthocyanins is attributed to their peculiar structure, namely the oxonium ion in the C ring (Van Acker *et al.*, 1996). Anthocyanin antioxidant have been attributed to aglycone moiety, the number of sugar residues at the 3-position, the oxidation state of the C ring (Wang *et al.*, 1999). Lee and Wicker (1991) reported that the two major anthocyanin contents of several mulberries cultivar are cyanidin-3-glucoside and cyanidin-3-rutinoside.

Neuroprotective activity

Numerous studies indicate the beneficial role of mulberry extracts for the treatment of oxidative stress-induced disorders in the brain. Mulberry leaf extract (MLE) reduces oxygen glucose

deprivation-induced cerebral ischemic condition and GABA depletion in the brain. Cyanidin-3-glycoside the most notorious and investigated among cyanidin-glycosides. Kang *et al.*, (2006) investigated of neuroprotective effects of the cyanidin-3-O-beta-D-glucopyranoside C3 G isolated from the fruits of *M. alba* against neuronal cell damage and cerebral ischemia. Flavonoids isolated from the fruits of *Morus alba* L; artoindonesianin O, isobavachalcone, morachalcone A, quercetin, astragalgin, isoquercetin, and rutin have neuroprotection effects on glutamate-induced oxidative injury in HT22 hippocampal cells (Seo *et al.*, 2014). Mulberroside A is a natural polyhydroxylated stilbene compound present at relatively high abundance in the roots and twigs of *Morus alba* L. Wang *et al.* (2014), show that mulberroside A have neuroprotective effects that can be used in the treatment of brain ischemic injury using primary culture of rat cortical neurons in vitro model. Mulberroside A has the ability to counteract the hypoxia-ischemia impairment and exhibiting anti-inflammatory and antiapoptotic effects. Another component, Oxyresveratrol is a potent antioxidant and free-radical scavenger found in mulberry wood (*Morus alba* L.) that demonstrated protective effects against cerebral ischemia (Weber *et al.*, 2012). Oxyresveratrol exert differential neuroprotective ability against two pathologies of high glutamate exposure and trauma.

Mulberry extracts and improvement of memory

Lead (Pb) a highly neurotoxic agent that affects the developing central nervous system is ubiquitous in the environment, and low-level Pb exposure can cause neurotoxicity and irreversible damage to children's cognition, learning and memory ability. Mulberry extract (ME) exhibited neuroprotective effects of against Pb-induced learning and memory deficits in mice, and restore NO production and anti-oxidant enzymes. MLE inhibits Pb-induced neurotoxicity by reversing Pb-induced alterations in the aspect of neurotoxic effects and improving learning and memory. Furthermore, anthocyanin-rich fruits have been described that show memory improvement efficacy in animal models (Andres-Lacueva *et al.*, 2005). The protective effect of mulberry fruit extract on memory impairment and brain damage in animal model of vascular dementia has been also regarded by Kaewkaen *et al.* (2012). Mulberry fruit extract improved oxidative status and increase Bcl-2 resulting in the increased densities of neurons and cholinergic neurons in hippocampus especially in CA3 that contribute the important role in associative memory function. *Morus Atropurpurea* supplementation, rich in phenolics and anthocyanins have been shown to have beneficial effects on prevention of Alzheimer disease and to be advantageous to the induction of an antioxidant defense system and for the improvement of memory deterioration in ageing and on the promotion of cognition in senescence-accelerated mice (Shih *et al.*, 2010).

Mulberry extract and depression

Depression is one of the most common mental disorders, affecting nearly 21% of the world's population (Schechter *et al.*,

2005). Depression is a pathophysiological process may be triggered by excessive and prolonged secretion of adrenal glucocorticoids. The antidepressant-like effects of the alcohol extract Cortex Mori Radicis (CMR) have been demonstrated by Lee *et al.*, 2013. Mulberry extract produced antidepressant-like effect through producing a downregulation of serine/threonine protein phosphatase 5 levels, leading to a strong negative relationship with pGR (S232).

Lim *et al.* (2014) demonstrated that *M. alba* EtOAc fraction have beneficial effects on depressive behavior. Ethyl acetate fraction of *M.alba* decreased the immobility time in rats exposed to the Forced Swim Test and decreased the hypothalamic –Pituitary –adrenal HPA response to the stress, as indicated by an attenuated corticosterone response and decreased c-fos immunoreactivity in the hippocampal and hypothalamic paraventricular nucleus (PVN) region.

Anti-aging effect

ROS are involved in aging, progressive neuronal death, and age related disorders (Sohal and Orr 2012). Polyphenols has the abilities to reduce inflammation and modulating the activity of intracellular signal transduction molecules in the brain (Choi *et al.*, 2012). The anti-aging effect of mulberry leaves extracts on the aging of model animals have been investigated by Zheng *et al.* (2014) which indicated that MLE extended the mean life span of *C. elegans*, improved oxidative stress resistance and regulate transcription factors and gene expression downstream of the germline signaling pathway in *Caenorhabditis elegans* in vivo model.

Anticonvulsant activity

Morus alba leaves methanolic extract showed protection against PTZ-induced convulsions. PTZ is a GABA-A receptor complex antagonist and produces seizures by the GABA pathway inhibition in the central nervous system due to the imbalance in ionic concentrations of the membrane. A finding supported by Gupta *et al.*, 2014 reveals that MLE exhibits potential antiepileptic activity via facilitation of GABA transmission

Chronic treatment with typical antipsychotics leads to the development of abnormal hyperkinetic orofacial movements (vacuous chewing movements, tongue protrusions and facial jerking) in rats and is widely accepted as the animal model for tardive dyskinesia.

Haloperidol is a typical neuroleptic that long –treatment plays an important role in the development of orofacial dyskinesia. A protective effect of *Morus alba* extract against haloperidol-induced orofacial dyskinesia and oxidative stress was assessed. Methanol extract of *Morus alba* Linn. Leaves on an animal model of tardive dyskinesia showed a marked effect on behavioral parameters altered by haloperidol treatment. Extract attenuated the increase in vacuous chewing movements and tongue protrusions induced by haloperidol (Nade *et al.*, 2010). Even further, these last Nade *et al.*, 2010 has been shown anti-stress effects of *Morus*

alba in chronic restraint stress (RS)-induced perturbations in behavioral, biochemical and brain oxidative stress status. Restraint stress is a well-known method to induce chronic stress which leads to alterations in various behavioral and biochemical parameters.

Mulberry extract and Parkinson diseases (PD)

Parkinson's disease (PD) is characterised by the loss of dopaminergic neurons in the substantia nigra pars compacta to the striatum. Epidemiological findings suggest that the consumption of fruits particularly of berries rich in anthocyanins and proanthocyanidins may reduce PD risk. Mulberry fruit from *Morus alba* L contains well-known antioxidant agents such as anthocyanins which protect dopaminergic neurons in toxin-induced Parkinson's disease models (Kim *et al.*, 2010). Extract of mulberry fruit exhibited a protective effect against neurotoxicity in *in vitro* and *in vivo* PD models. Mulberry extract protects SH-SY5Y cells stressed with 6-hydroxydopamine (6-OHDA) and this neuroprotective effect of ME was mediated by its antioxidant and anti-apoptotic effects, regulating reactive oxygen species and NO generation, Bcl-2 and Bax proteins, mitochondrial membrane depolarisation and caspase-3 activation. In the sub-acute mouse PD model induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), mulberry extract (ME) showed a preventative effect against PD-like symptoms (bradykinesia) in the behavioural test and prevented MPTP-induced dopaminergic neuronal damage in an immunocytochemical analysis of the substantia nigra pars compacta to the striatum.

Recent findings suggest that PD risk increases as a result of chronic exposure to environmental pollutants. Administration of rotenone, a potent rotenoid used in insecticides, has been used as a model of Parkinson's disease; it has been shown to result in the systemic inhibition of mitochondrial complex I activity, which leads to the degeneration of dopaminergic neurons within the substantia nigra and striatum (Yang *et al.*, 2006). Chinese mulberry (*Morus alba*) extract rich in anthocyanins and proanthocyanidins is able to alleviate neurodegeneration in PD via enhancement of mitochondrial function (Strathearn *et al.*, 2014). Other study revealed that an oxyresveratrol (oxy) a polyhydroxylated stilbene -rich mulberry extract alleviated rotenone neurotoxicity in primary midbrain cultures and attenuated neuronal cell death triggered by PD-related insults in cellular or animal models (Khan *et al.*, 2010). Even further, due to its antioxidant activity and blood-brain barrier permeability, oxyresveratrol shows to exert neuroprotective effects against parkinsonian mimetic 6-hydroxydopamine (6-OHDA) neurotoxicity via phosphorylation of JNK and c-Jun and increasing the basal levels of SIRT1 (Chao *et al.*, 2008).

Previous studies have shown that monomeric proanthocyanidin such as catechin and epigallocatechin-3-gallate and extract rich in these polyphenols, are neuroprotective in cellular and rodent models of PD (Choi *et al.*, 2002; Guo *et al.*, 2007; Levites *et al.*, 2002). Catechin may protect brain against Peroxynitrite induced formation of the neurotoxins 5-S-cysteinyl-

dopamine, an endogenous neurotoxin involved in the onset of Parkinson's disease (Vauzour *et al.*, 2008).

In addition, other studies indicate that catechin derivatives may delay the onset of neurodegenerative disorders through a number of different mechanisms such as iron chelators, radical scavengers, and modulators of pro-survival genes.

Ishige *et al.* (2001) found that flavonoid protection against glutamate toxicity was dependent on the degree to which the substance is able to enter the cell. These findings were in accordance with those supported by Pavlica *et al.* (2010) who suggested that the presence of catechol group in flavonoid metabolites was sufficient to exert antioxidative and scavenging activities. Neuroprotective effects of the parent flavonoid were mimicked to a greater degree by the lipophilic metabolite, emphasizing lipophilicity as a determinant in the overall degree of flavonoid protection to neuronal cells.

Mulberry extract and Alzheimer disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder, affecting millions of people worldwide. It is known that mulberry leaves exert anti-amyloidogenic action and neuroprotective effects against $A\beta$ peptides. *Morus nigra* mulberry fruits completely reverse $A\beta_{25-35}$ -induced neuronal injury, counteract ROS formation, and inhibit apoptosis. Mulberry extract downregulated mRNA levels of Apoptotic protease-activating factor (Apaf1) and the changes of transcription level of which may associate with the development of AD. ME also inhibits $A\beta_{25-35}$ -induced upregulation of Bace2 mRNA expression which exhibits β -secretase-like activity, a key enzyme in the production of the amyloid- β peptide ($A\beta$) and is thought to be involved in Alzheimer's disease (AD) pathogenesis. These findings proved that the bioactive components in ME can inhibit cell apoptosis, $A\beta$ formation, or membrane damage-associated gene expression (Song *et al.*, 2014).

It has been reported that quercetin is the most abundant flavonol glycoside and the greatest contributor to antioxidant activity in mulberry leaves (Katsube *et al.*, 2009). Pretreatment of primary hippocampal cultures with quercetin significantly attenuates $A\beta$ -induced toxicity, lipid peroxidation, protein oxidation and apoptosis (Ansari *et al.*, 2009).

In addition, numerous studies indicate that catechin derivatives may delay the onset of neurodegenerative disorders such as Alzheimer's disease through a number of different mechanisms such as iron chelators, radical scavengers, and modulators of pro-survival genes. A novel phenolic compound from mulberry, artoindonesianin O (AIO) exerts neuro-protection by blocking oligomer $A\beta_{42}$ - or NMDA -induced neurotoxicity and pKadaic acid induced tau protein hyperphosphorylation through inhibiting the expression of kinase p-ERK1/2. AIO is suitable and possible candidature for the development of general food type neuroprotection on AD by protecting against brain damage and memory impairment and synaptic plasticity (Qiao *et al.*, 2015).

Hypercholesterolemia and altered cholesterol metabolism are associated with increased oxidative stress and the development of neurotoxicity and Alzheimer's disease. Cholesterol is a major constituent, derived by de novo synthesis and the blood-brain barrier. Cholesterol is tightly regulated between neurons and glia—that is, astrocytes, microglia, and oligodendrocytes and is essential for normal brain development. Enzymatic production of the beta amyloid peptide, the peptide thought to play a major role in AD pathogenesis, is affected by membrane cholesterol levels. El-Sayyad HI (2015) has been found that *Morus alba* leaves, fruit, and bark improved brain function and reduce low-density-lipoprotein cholesterol level and can act as antilipidemic drugs and prevent cholesterol neurotoxicity

Mulberry rich-polyphenols and brain infection

Bauomy (2014) investigate the potential role of mulberry extract on the brain on mice infected with *Schistosoma mansoni*. Schistosomiasis is a tropical disease which is associated with neuropsychiatric and neuropathological disorders. Schistosomiasis induced brain oxidative stress as evidenced by the decrease of glutathione level, total antioxidant capacity and the activity of catalase significantly, while a significant elevation in the levels of nitrite/nitrate and malondialdehyde. Besides, this disease infection is resulted in neurochemical disturbances and characterized by; the decreased level of inhibitory amino acid, γ -aminobutyric whereas the level of chloride ions and acetylcholine esterase activity were significantly increased. Impairments in the brain are also detected. In this case, the treatment with mulberry extract ameliorated the induced disturbances in schistosome-infected mice where the levels of non-enzymatic and enzymatic antioxidants were elevated. ME reduce the levels of nitrite/nitrate and malondialdehyde, improved the altered levels of γ -aminobutyric acid level and chloride ion and improved the recorded impairments of the histopathological section in the brain of schistosome infected mice (Bauomy *et al.*, 2014)

CONCLUSION

There is growing evidence that dietary polyphenols may play an important role to suppress oxidative stress and preventing neurodegenerative disorders. Mulberry rich polyphenols appear to be a good candidate for neuroprotection and treatment of oxidative stress-induced disorders in the brain and there to prevent age-related neurodegeneration.

Bioactive components in mulberry extract exert strong antioxidative potential protecting against brain damage. The effects of the mulberry extract in animals model and patients with brain disorders such as AD, PD will be investigated and underline the evidence for a neuroprotective effect of antioxidants in the treatment of neurodegenerative disorders in humans.

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