

## Neurodegenerative Diseases and Phytochemicals

### *Nörodejeneratif Hastalıklar ve Fitokimyasallar*

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#### ABSTRACT

Neurodegeneration is defined as the progressive loss of neurons, either structurally or functionally. Alzheimer's (AD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Huntington's (HD), and Parkinson's (PD) are the most important neurodegenerative diseases. Genetic factors, amyloid plaque formation, neurofibrillary tangles, mitochondrial dysfunction, and trauma are all factors involved in the etiopathogenesis of these diseases. Additionally, it has been suggested that neurodegenerative diseases are most likely associated with oxidative stress and neuroinflammation. Various studies have shown that phytochemicals found in fruits, vegetables, nuts, oil seeds, and whole grains have anti-inflammatory, antioxidant, and anti-apoptotic mechanisms of action. Phytochemicals may exert neuroprotective effects through these mechanisms, thus contributing to slowing the progression of diseases. In this review, the effects of phytochemicals with antioxidant and anti-inflammatory effects on neurodegenerative diseases were investigated.

*Keywords: Neurological diseases, Phytochemicals, Neuroinflammation, Oxidative stress*

#### ÖZET

Nörodejenerasyon, yapısal veya fonksiyonel olarak nöronların ilerleyici kaybı olarak tanımlanır. Alzheimer (AD), Multipl Skleroz (MS), Amiyotrofik Lateral Skleroz (ALS), Huntington (HD) ve Parkinson (PD) en önemli nörodejeneratif hastalıklardır. Genetik faktörler, amiloid plak oluşumu, nörofibriler yumaklar, mitokondriyal disfonksiyon ve travma bu hastalıkların etyopatogenezinde rol oynayan faktörlerdir. Ayrıca nörodejeneratif hastalıkların oksidatif stres ve nöroinflamasyon ile bağlantılı olduğu ileri sürülmektedir. Meyveler, sebzeler, kuruyemişler, yağlı tohumlar ve tam tahıllarda bulunan fitokimyasalların antiinflamatuvar, antioksidan ve anti-apoptik etki mekanizmalarının olduğu çeşitli çalışmalarda gösterilmiştir. Fitokimyasallar bu mekanizmalar yoluyla nöroprotektif etkiler gösterebilir, böylece hastalıkların prognozunu yavaşlamasına katkıda bulunabilir. Bu derlemede, antioksidan ve antiinflamatuvar etkileri olan fitokimyasalların nörodejeneratif hastalıklar üzerine etkileri araştırılmıştır.

*Anahtar kelimeler: Nörolojik hastalıklar, Fitokimyasallar, Nöroinflamasyon, Oksidatif stres*

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## INTRODUCTION

Neurodegenerative diseases are among the leading causes of death worldwide after cancer and cardiovascular diseases. Unless new treatment approaches are developed, mortality from neurodegenerative diseases is expected to be the first (1). Neurodegenerative diseases are the general name given to chronic and progressive diseases that cause deterioration of nervous system functions as a result of damage to nerve cells and some parts of the brain. Amyloid plaques, which are one of the factors suggested to play a role in the etiopathogenesis of these diseases, are the accumulation of extracellular  $\beta$ -amyloid protein, while neurofibrillary tangles, another factor, occur as a result of hyperphosphorylation and misfolding of Tau protein in the cell. In addition to these, oxidative stress, mitochondrial dysfunction, ischemia, neuroinflammation, genetic mutations, endoplasmic reticulum cellular stress, cholinergic dysfunction, axonal transport chain disorders, neuronal apoptosis caused by various causes, impaired microglial cell activation, excitotoxicity, and neurotoxicity are among other etiopathogenetic factors (1,2).

Alzheimer's (AD), Parkinson's (PD), Huntington's (HD), Amyotrophic Lateral Sclerosis (ALS), and Multiple Sclerosis (MS) are among the most important and common neurodegenerative diseases. While the pathological and physiological findings of these diseases vary, the cellular mechanisms involved in disease development are similar (2). In these diseases, it has been shown that reactive oxygen species (ROS) cause neurodegeneration by increasing oxidative stress and apoptosis in neurons (3). Causes such as the accumulation of free radicals, decreased capacity of cells to maintain redox balance, and mitochondrial dysfunctions are especially effective in the formation of age-related neurodegenerative damage (4). In addition, neuroinflammation is one of the factors that cause neuronal dysfunction and mental deterioration by causing an increase in inflammatory cytokine and chemokine production (5). Drugs used in the treatment of neurodegenerative diseases do not

provide a definitive treatment but only act to slow the progression of the disease. For this reason, various plants and phytochemicals with antioxidant and anti-inflammatory potential are shown to prevent neurological diseases and alleviate neurological symptoms in clinical studies (5,6).

### Neurodegenerative Diseases and Oxidative Stress

Oxidative stress (OS) is a condition in which the balance between antioxidants and ROS is disturbed towards ROS in healthy cells (7). OS is associated with many neurodegenerative diseases, including AD, PD, HD, MS, and ALS (8). In these diseases, an increase in OS may be observed due to the depletion of antioxidants, mitochondrial dysfunction, neuroinflammation, and an increase in proapoptotic protein expression (9). With increased OS, an excessive amount of ROS is produced, causing deoxyribonucleic acid (DNA) damage and cell cycle abnormalities, leading to neurodegeneration (10). The nervous system, the brain, and consequently the neurons, are highly sensitive to oxidative stress. Many reasons may explain this sensitivity: Polyunsaturated fatty acids that are sensitive to ROS and susceptible to oxidation, constitute a large part of the lipids of the cerebral cortex (4). Neurons produce much more adenosine triphosphate (ATP) through oxidative phosphorylation than other cells. Oxidative phosphorylation increases the formation of oxidative stress because it is a reaction that causes large quantities of ROS leakage (11). Although the brain accounts for 5% of body weight, it uses almost 20% of the inhaled oxygen, leaving it exposed to high concentrations of oxygen. Under physiological conditions, 1-2% of inhaled oxygen is converted into ROS, causing oxidative stress (12). The transition metals that act as powerful catalysts for ROS formation in the brain are abundant. The presence of iron, especially in areas such as the substantia nigra, leads to an increase in the production of ROS transition metals. In addition, enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, which play a role in the detoxification

of ROS, are known to be present in the brain at low to moderate levels (4). The brain is protected by the blood-brain barrier because of its high sensitivity and functional importance (13). Due to its selectively permeable structure, the blood-brain barrier prevents toxins and other macromolecules from passing through the blood to the brain. It has been reported that OS causes damage to the blood-brain barrier by damaging various types of cells (such as pericytes and astrocytes). This situation plays a major role in the development of various neurodegenerative diseases (14). Especially in the development of age-related neurodegenerative conditions, causes such as the accumulation of free radicals, decreased capacity of cells to maintain redox balance, mitochondrial dysfunctions, a decrease in glutamate transporters and neuronal glucose transporter 3 (GLUT3) cause neuronal damage and play a role in the formation of neurodegenerative diseases (4).

### **Neurodegenerative Diseases and Neuroinflammation**

Inflammation is a reaction created by the immune system to protect the body from various diseases or injuries. Neuroinflammation is a complex event associated with the activation of microglia, astrocytes, and blood-brain barrier endothelial cells in the brain tissue, and the migration of plasma proteins and immune system cells to the brain tissue by crossing the impaired blood-brain barrier and the release of cytokines. In short, this is the activation of the brain's immune system and is characterized by a series of cellular and molecular changes. Microglial cells differ from myeloid stem cells in embryonic life and are responsible for the production of cytokines and chemokines with their macrophage-like properties (15). Neuroinflammation that occurs in the central nervous system can support or damage the immune system. Controlled neuroinflammation is valuable and beneficial for the host's immune response. For example, stimuli mediated by interleukin-1 (IL-1) and interleukin-4 (IL-4) cytokines facilitate neuronal

plasticity in processes such as brain development and learning, and IL-4 released as a result of trauma contributes to axonal regeneration and tissue damage repair. However, uncontrolled inflammation produces free radicals that cause oxidative stress (16). Although neuroinflammation is partially an adaptive mechanism, long-term inflammation is associated with long-term neurodegeneration (17). The aim of inflammation treatment is to limit neuroinflammation to the level where it is beneficial while preventing chronic inflammation over the long term (18). Therefore, when assessing neuroinflammation, activated cells, synthesized cytokines, released free radicals, and brain damage should be considered as a whole (16).

### **The Relationship Between Neurodegenerative Diseases and Phytochemicals**

Phytochemicals are bioactive substances found in edible plants such as fruits, vegetables, seeds, nuts, and cereals that have been shown to exhibit health benefits such as antioxidant, antimicrobial, anti-inflammatory, and anticancer effects, and substances that are taken daily or rarely, exhibiting the potential to modulate human metabolism in a way suitable for the prevention of chronic and degenerative diseases (19). Phytochemicals are considered promising therapeutic agents in various diseases, including neurodegenerative disorders, as well as show a wide range of neuroprotective efficacy through various mechanisms of action, including anti-inflammatory, antioxidant, anti-apoptotic, and direct neuroprotective effects (20). Many phytochemicals are known to positively affect various neurological disorders through neuroprotective mechanisms. The lack of an effective therapeutic strategy to manage neurodegenerative diseases increases the interest of individuals in herbal medicine, where phytochemicals have an important role because phytochemicals have been used in traditional medicine since time immemorial (21).

Natural phytochemicals may be less toxic than new synthetic drugs. However, since these traditional herbal remedies are usually prepared from raw materials, many questions are asked about their specific medicinal effects and reproducibility, mechanisms of action, and identity of the active ingredients (22). For this reason, recent research has focused on the specific active compounds of a plant rather than on the whole plant. However, due to their potential therapeutic effects on neurodegenerative diseases, certain active ingredients need to be identified and characterized (23). Several phytochemicals, including curcumin, apigenin, genistein, quercetin, resveratrol, and epigallocatechin gallate, have been studied in many studies that have shown neuroprotective effects against various neuroinflammatory disorders in experimental studies (24). These effects are shown in Table 1 as a summary.

Curcumin, with its antioxidant and anti-inflammatory properties, has a neuroprotective effect in neurodegenerative diseases. Clinical studies have shown that curcumin can prevent PD, reduce

cyclooxygenase-2 expression caused by ROS in ALS, improve symptoms of MS and other brain injuries, and also suppress the overexpression of inflammatory mediators in neuroinflammation. For example, in transgenic mice with AD, curcumin effectively affects p25-mediated glial activation and proinflammatory chemokine/cytokine production in the healing of cognitive impairments (29). Recently, conjugated curcumin, such as nanocurcumin or curcumin-like analogues, have been developed to increase their bioavailability and potential neuroprotective activity in PD. Although the therapeutic effect of curcumin for neurodegenerative diseases has been increasingly studied, evidence of metabolism, safety, tolerance, bioavailability, and even in vivo metabolic evidence, including its pharmacokinetics, metabolism, safety, tolerance, bioavailability, and even entry into the blood-brain barrier, has still not been fully reported (30). Curcumin is usually regarded as safe, while some animal studies have revealed that very high dosages may cause gastrointestinal ulcers, thyroid follicular cell hyperplasia, and hepatotoxicity.

**Table 1.** Phytochemicals' major effects on neurodegenerative diseases and maximum adult daily intakes

Resources	Phytochemicals	Suggested Benefits and Effects on Neurodegenerative Diseases (25)	Adult Daily Intake (Maximum)
Turmeric	Curcumin	1) Anti-oxidant 2) Anti-inflammatory 3) Mitochondrial protection 4) Anti-apoptotic 5) Anti-aggregation effect	600 mg/day (26) 3 mg/weight/day (27)
Grapes, Grape Juices and Wine	Resveratrol	1) Anti-oxidant 2) Anti-inflammatory 3) Mitochondrial protection 4) Anti-apoptotic 5) Anti-aggregation effect	5 g/day (26) 150 mg/day (28)
Fruits, Vegetables	Apigenin	1) Anti-Inflammatory	Not reported
Fruits, Vegetables	Quercetin	1) Anti-oxidant; 2) Anti-inflammatory 3) Mitochondrial protection 4) Anti-apoptotic 5) Anti-aggregation effect	500 mg/day (26)
Green tea	Epigallocatechin-3-gallate (EGCG)	1) Anti-oxidant 2) Mitochondrial protection 3) Anti-apoptotic 4) Anti-aggregation effect	540 mg/day (26)

Even though it is obvious that curcumin has a wide range of therapeutic effects, not all research supports this encouraging picture. For instance, curcumin promoted lung carcinoma in one animal study (31). In human trials, 1200 mg of curcumin per day was generally well tolerated; however, two of the 19 patients who received this dosage had stomach discomfort in one study. Curcumin was shown to be well tolerated at dosages up to 8 g/day in another trial; however, larger doses were not tolerated merely because of the agent's size (22). According to the list of dietary supplements restricted substances of the Ministry of Agriculture and Forestry of the Republic of Turkey, the maximum dose of food supplement curcumin is 600 mg/day for adults ( $\geq 11$  years old) (26).

As a neuroprotective agent, resveratrol is known to suppress the overexpression of inflammatory mediators in activated microglia and astrocytes. In lipopolysaccharide-induced cortical neurotoxicity, resveratrol has been shown to significantly protect cortical neurons against neuroinflammation by inhibiting microglia activation, followed by the production of proinflammatory and cytotoxic factors such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), nitric oxide, and interleukin-1  $\beta$  (IL-1  $\beta$ ) (32). In mice with intracerebral haemorrhage, treatment with resveratrol is known to reduce acute neurological deficits, neurodegeneration, and cerebral edema, while concomitantly resulting in a reduction in IL-1  $\beta$  expression (33). In another study, whole-genome microarray analysis showed that in high-fat/high-sugar (HFS) stress-impaired red-cheeked monkeys, dietary (2 years) administration of resveratrol differently modulated and improved a range of genes and pathways linked to vascular health and inflammation in the cerebral cortices (34). An epidemiological study shows that a moderate intake of resveratrol-rich red wine can counteract oxidative stress and metal ion deregulation produced by amyloid and metal dysmetabolism in the brains of individuals with AD (35). Resveratrol has been shown to have a more beneficial effect in therapeutic action in counteracting neurodegenerative diseases, being

an active scavenger of free radicals and a modulator of prosurvival or proinflammatory signalling pathways (30). The relative safety of resveratrol was investigated, with short-term or acute administration of single or repeated doses (25 mg to 5 g/day) resulting in minimal or inconsistent adverse effects, but not enough toxicity of resveratrol for chronic consumption was documented (36). A 150 mg/day dosage of resveratrol as a food supplement in capsule or tablet form was reported to be a safe amount for adults by the Panel on Dietetic Products, Nutrition and Allergies. The Panel notes that diarrhoea or other gastrointestinal problems were recorded in four uncontrolled intervention trials at dosages of 1 g resveratrol/day or higher (28).

Tumour necrosis factor- $\alpha$ , a key target that can modulate the pathology of a large number of neurological disorders, has attracted great attention in the recent past. More studies are included in this sense in order to obtain TNF- $\alpha$  inhibitors/blockers from natural products and nutraceuticals. TNF- $\alpha$  inhibitors/blockers are thought to be an alternative way to treat disorders in which TNF- $\alpha$  plays a key role. Many phytochemicals, such as turmeric, shogaol, paradol, and equol are known to have very important roles in inhibiting TNF- $\alpha$  with fewer side effects (21). Recent findings have suggested that phytochemicals such as allyl isothiocyanate (AITC), quercetin, and kaempferol have the potential to control neuronal disorders by inhibiting TNF- $\alpha$  production. In addition, apigenin, naringenin, and myristicin have been shown to inhibit various inflammatory disorders by significantly inhibiting TNF- $\alpha$  expression. In addition, TNF- $\alpha$  has been found to be one of many phytochemicals that exhibit anti-inflammatory activity through inhibition of its binding and activity or through direct inhibition. Most of these phytochemicals inhibit the production of TNF- $\alpha$ . Similarly, phytochemicals such as nicotine, berberine, capsaicin, and kavalactone are important factors for the inhibition of inflammation in the development of Alzheimer's disease and Parkinson's disease by inhibiting TNF- $\alpha$ . The diallyl sulphide found in *Allium sativum* has also been reported to

have a strong anti-inflammatory effect, reducing the production of proinflammatory cytokines such as TNF- $\alpha$  (37).

Neurotrophins are important for the survival, preservation, and regeneration of specific neuronal populations in the brain. Neurotrophins, defined as proteins that support neuronal life in mammals, include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4/5. The decrease in neurotrophins has been associated with the pathology of several neurodegenerative diseases and their physiological symptoms. In the studies conducted accordingly, the decrease in neurotrophins has been associated with the pathology of several neurodegenerative diseases and their physiological symptoms. It is thought that the administration of neurotrophin may be an effective treatment for neurodegenerative diseases. Quercetin, a flavonoid, sweeps away free radicals through its antioxidant properties and plays a protective role in neurons from OS. Thus, quercetin helps to support activity in the hippocampus, which regulates neuronal survival rate (23). The maximum quercetin intake for adults ( $\geq 11$  years old) is specified as 500 mg/day in the Republic of Turkey dietary supplements restricted substances list (26). Rarely, it can cause mild gastrointestinal discomfort (38). Recently, a lot of work has been carried out on apigenin, and it has been found that it also plays a vital role in neurodegenerative diseases. Apigenin exerts its anti-inflammatory effect on microglia, is activated by lipopolysaccharide, and removes free radicals. In addition, apigenin has a significant coefficient of permeability in the blood-brain barrier and therefore serves as an effective phytochemical for the treatment of neurodegenerative diseases. It offers an extensive discussion of the literature on phytochemicals and shows that these compounds offer a safe approach to protecting against neuronal damage caused by neurotrophin deficiencies and toxin-induced degenerative diseases (23). Apigenin's rapid rate of metabolism and low bioavailability required optimal dosages for its desired impact, as

evidenced by many clinical investigations. This also restricts the use of apigenin to improve human health, which may be enhanced by investigating its functions in more models (39).

The major bioactive compound of green tea, EGCG, has the potential to treat neurodegenerative diseases. EGCG targets protein misfolding and aggregation, which is a prevalent cause and pathogenic process in many neurodegenerative disorders. EGCG interacts with misfolded proteins such as synuclein, connected to PD, and amyloid beta-peptide, linked to AD. EGCG is typically well tolerated, but it has been linked to hepatotoxic effects in some individuals; thus, high doses should be avoided (40). According to the list of dietary supplements restricted substances of the Ministry of Agriculture and Forestry of the Republic of Turkey, the maximum dose of food supplement EGCG is 540 mg/day for adults ( $\geq 11$  years old) (26).

## CONCLUSION

Neurodegenerative diseases that occur with the folding and proteasomal disorders of certain proteins due to environmental and genetic factors, contributing to the development of mitochondrial dysfunction, oxidative stress, and neuroinflammation, affect individuals and society to a great extent. Neurodegenerative diseases can cause irreversible dysfunction in nervous system. Many dietary plant components have been shown to cross the blood-brain barrier and reduce or prevent the risk of neurodegenerative diseases, thus providing therapeutic benefits to patients. It has been suggested that neurodegeneration can be slowed down by the use of phytochemicals that have anti-inflammatory and anti-inflammatory effects against neuroinflammation and OS, and that natural compounds can inhibit these effects largely due to their potent poor pharmacokinetic properties. In the treatment of neurodegenerative diseases, phytochemicals alone may not have an absolute effect, but they can serve to prevent and delay the onset of neurodegenerative diseases. In addition to this situation, phytochemicals do not appear to

be cytotoxic according to their chemical structure; they provide the appropriate environment for the care of mature neurons and provide the renewal of neurons. Studies should be carried out to determine the appropriate amounts and mechanisms of action of phytochemicals to be used in neurodegenerative diseases and to be effective and not cause toxicity.

Neuroprotective phytochemicals are appealing alternatives to drugs such as NSAIDs and anti-degenerative molecules, which lack conclusively demonstrated clinical efficacy and are associated with significant safety concerns. Although there are apparent limitations to its immediate broad application, dietary polyphenolic phytochemicals show enormous promise as safe, affordable, and easily accessible preventive treatments for neurodegenerative diseases. Next generation studies should focus on to achieve the potential of these compounds with further efforts to extrapolate in vitro and in vivo outcomes to human cases through properly planned clinical studies. The maximum values given in the supplementary foods restricted substances list of the Ministry of Agriculture and Forestry of the Republic of Turkey should not be exceeded. In addition, food supplements should be labelled and inspected in accordance with the rules defined in regulations and communiqués.

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