Application of flavonoids for the protection of nigral dopaminergic neurons from oxidative stress

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Oxidative stress in Parkinson's disease (PD): Oxidative stress is the imbalance between oxidants, which generate reactive oxygen species (ROS; free radicals), and antioxidants, which remove free radicals. Under healthy conditions, the levels of oxidants and antioxidants are well-balanced. However, excessive production of ROS and a deficiency of antioxidants leads to oxidative stress, which may be the cause of accelerating the development of neurodegenerative diseases (Hwang, 2013), suggesting that the prevention of ROS production and reduction of oxidative stress is critical for both the prevention and treatment of neurodegenerative diseases, including PD.

PD is a chronic and gradual progressive neurological disease that is associated with the loss of dopaminergic (DA) neurons in the substantia nigra (SN) in the adult brain, resulting in decreased striatal dopamine levels (Leem et al., 2016; Jung and Kim, 2018). These changes lead to many clinical symptoms such as rigidity, resting tremor, and bradykinesia. The pathogenic mechanisms of PD displaying the degeneration of the nigrostriatal DA system remain unclear. Nonetheless, the upregulation of risk factors is involved in the pathogenesis and progression of PD (Kim et al., 2011; Leem et al., 2016; Jung and Kim, 2018). Particularly, oxidative stress, leading to cellular dysfunction and death, is a key risk factor of PD because of the vulnerability of DA neurons to oxidative stress (Hwang, 2013; Leem et al., 2016; Jung and Kim, 2018).

Major sources of ROS generation in the SN: Excessive production of ROS in the SN primarily results from abnormal cellular conditions, including mitochondrial dysfunction, exceptional dopamine metabolism, and neuroinflammation (Jung and Kim, 2018; Weng et al., 2018; Ammal Kaidery et al., 2019).

Mitochondria produce energy for cellular metabolism through the oxidative phosphorylation system. Oxidative phosphorylation occurs throughout the electron transport chain, which comprises four protein complexes (complex I, II, III, and IV) present in the inner mitochondrial membrane, and through chemiosmosis via adenosine triphosphate (ATP) synthase, which is located in the inner mitochondrial membrane (Johri and Beal, 2012). The ATP synthase converts adenosine diphosphate (ADP) into ATP by utilizing the proton (H^+) gradient, existing across the inner mitochondrial membrane, and ATP is a high-energy molecule that generates energy for various life-sustaining activities in living cells, such as neuronal aerobic respiration. This process is called oxidative phosphorylation, with oxidative phosphorylation system and electron transport chain complexes I and II being the chief producers of ROS, such as hydrogen peroxide and superoxide anion, and it is enhanced when the electron transfer is reduced by the increased membrane potential. By means of electron leakage, oxygen interacts with unpaired electrons induced by nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) at complex I and produces superoxide anion. Subsequently, superoxide anion forms hydrogen peroxide via mitochondrial superoxide dismutase, and this ROS is released into the cellular cytosol and nucleus, causing oxidative stress. Hydrogen peroxide is then converted to hydroxyl radical by the Fenton reaction, leading to more oxidative stress (Schieber and Chandel, 2014). Furthermore, the reduction in complex I activity has been demonstrated in the SN of patients with PD (Gandhi and Abramov, 2012).

Dopamine is a representative neurotransmitter in DA neurons, which has a crucial role in motor activity. L-3,4-dihydroxyphenylalanine (L-DOPA) is synthesized from the amino acid tyrosine by tyrosine hydroxylase, and dopamine is synthesized from L-DOPA by DOPA decarboxylase. Although dopamine itself is not neurotoxic, specific dopamine metabolism, including the production of H_2O_2 by monoamine oxidase, generation of the superoxide radical, and degradation of cellular NADPH oxidase by dopamine-quinone, which is a highly reactive oxidized dopamine, can cause damage to DA neurons (Hwang, 2013).

Neuronal loss in PD is also related to neuroinflammation, which is chiefly controlled by microglia (Leem et al., 2016; Jung and Kim, 2018). Microglia are glial cells that serve as the first and most important form of active immune defense in the central nervous system. Under normal conditions, inactive microglia are in the resting state, maintaining the morphology of small cell bodies with ramified processes. However, under neuropathological conditions, microglia are activated, resulting in morphological changes such as large cell bodies with short or no processes, and activated microglia generate many inflammatory mediators and ROS, which are neurotoxic to the brain (Leem et al., 2016; Jung and Kim, 2018). In the SN of patients with PD, microglial activation has been well observed (Leem et al., 2016; Jung and Kim, 2018). Moreover, because the midbrain has more microglia than other brain regions, DA neurons would be more vulnerable to microglia leading to progressive DA neuron loss in PD owing to oxidative stress (Qian et al., 2010). Thus, reducing high levels of ROS and inflammatory mediators by controlling glial activation may prevent the degeneration of DA neurons in the SN.

Antioxidative effects of flavonoids for protection of DA neurons: As mentioned earlier, a part of the PD pathogenesis is associated with oxidative stress induced by mitochondrial dysfunction, dopamine metabolism, and neurotoxic inflammation (Qian et al., 2010; Gandhi and Abramov, 2012; Schieber and Chandel, 2014; Leem et al., 2016; Jung and Kim, 2018). Therefore, flavonoids, having potent free radical scavenging activity, have been considered dietary supplements that prevent and suppress PD pathogenesis.

Flavonoids are among the largest families of plant-derived phenolic compounds and are commonly found in foods and beverages of plant origin (Brunetti et al., 2013; Thilakarathna and Rupasinghe, 2013). The chemical structure of flavonoids allows various substitutions in their backbone, resulting in the production of various derivatives, and contributes to numerous biological activities, including antiallergenic and anti-inflammatory actions (Brunetti et al., 2013; Thilakarathna and Rupasinghe, 2013; Jung and Kim, 2018). Particularly, flavonoids can serve as antioxidants by themselves because of their ROS scavenging activity, which is derived from their chemical feature (Jung and Kim, 2018), and numerous flavonoids can control the redox imbalance by regulating the antioxidant enzyme genes (Jung and Kim, 2018). Recently, numerous studies

demonstrated the potential of flavonoids as preventive or therapeutic agents against the loss of DA neurons, which are vulnerable to oxidative stress, in different models of PD (Jung and Kim, 2018). The representative bioactivity of flavonoids, plant-derived phenolic compounds, is antioxidative effects. However, apart from the antioxidative effects, numerous flavonoids preserve the nigrostriatal DA pathway by exerting other antiparkinsonian effects, including antiapoptosis, anti-inflammation, and neurotrophic supports (Jung and Kim, 2018).

Conclusion: Oxidative stress results from an imbalance between the production of ROS and anti-oxidative defense system, which detoxifies and repairs the cytotoxicity caused by spare electrons and ROS (Jung and Kim, 2018). Oxidative stress is frequently referred to as a risk factor of pathogenesis involved in various diseases. In the SN of the adult brain, ROS production particularly occurs owing to mitochondrial dysfunction, catecholaminergic metabolism, and excessive neuroinflammation (Qian et al., 2010; Gandhi and Abramov, 2012; Hwang, 2013; Leem et al., 2016; Jung and Kim, 2018; Weng et al., 2018; Ammal Kaidery et al., 2019). Additionally, DA neurons have a striking vulnerability for the oxidative stress-related neurotoxicity, proposing that the maintenance of redox balance is a key factor for neuronal survival in the SN.

Flavonoids induce protective effects against neurodegeneration through the suppression of α-synuclein aggregation, induction of neurotrophic factors, and inhibition of neurotoxic inflammation in PD models *in vivo* and *in vitro* (Jung and Kim, 2018), and previous studies have indicated that a flavonoid-abundant diet can suppress the onset of PD among individuals who are at risk for oxidative stress by maintaining redox balance, suggesting that the dietary supplementation of flavonoids promotes beneficial health effects against PD (**Figure 1**). To use flavonoids as therapeutic agents against PD, whether the flavonoids contribute to protection and restoration of neuronal function and neurite outgrowth in humans should be clarified. In addition, it is necessary to clarify effective methods related to dietary supplements of flavonoids, including the concentration and route of treatment, and to investigate the hormetic dose of each flavonoid and understand the hermetic effects and mechanisms in order to prevent the unexpected responses preceding clinical trials against PD (Di Rosa et al., 2020). However, although no experimental result is directly associated with patients with PD, previous reports support the proposal that dietary supplementation of flavonoids could be an alternative strategy for the prevention and treatment of PD.

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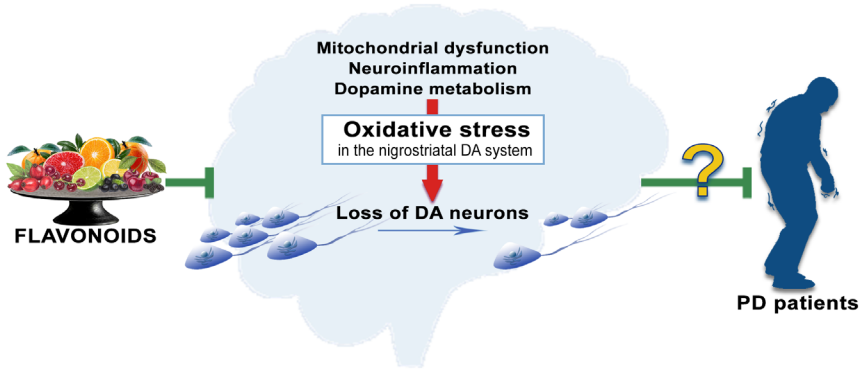

Figure 1 | **Potential of flavonoid administration for protection of nigral DA neurons from oxidative stress in the adult brain.**
The excessive production of reactive oxygen species in the substantia nigra, resulting from abnormal cellular condition, including mitochondrial dysfunction, neuroinflammation, and exceptional dopamine metabolism, is among the major causes of the degeneration of DA neurons in the adult brain, and the loss of DA neurons can be associated with the pathogenesis and progression of PD. The health-promoting bioactivities of flavonoids, such as antioxidative, anti-inflammatory, and antineurotoxic effects, are well clarified. Recently, numerous studies indicated that a flavonoid-abundant diet, inhibiting oxidative stress and neuroinflammation in the adult brain, may be useful to suppress neurodegeneration associated with neurodegenerative diseases. Therefore, although there is no clinical report on the therapeutic effects of flavonoid administration in PD, these recent reports demonstrate that the dietary supplementation of flavonoids may induce beneficial health effects against PD. DA: Dopaminergic; PD: Parkinson's disease.

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