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Potential benefits of specific nutraceuticals in Parkinson's disease model in rats

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Parkinson's disease (PD) is one of the most common neurodegenerative diseases, which comes in second place in terms of prevalence after Alzheimer's disease. The rate of incidence of PD increases with the advancement of age. Searching for nutraceuticals for the management of PD is a good approach since, so far, there is no efficient drug for such a disease. In addition, an interrelation of the immune system and iron status in PD is an important issue to be studied. In this context, a question arises: do the nutraceuticals that can improve the disease may also enhance the iron status?

The research entitled "Iron status, immune system, and expression of brain divalent metal transporter 1 and dopamine receptors D1 interrelationship in Parkinson's disease and the role of grape seed and green coffee bean extracts and quercetin in mitigating the disease in rats" newly published in the Journal of Herbmed Pharmacology studied the role of nutraceuticals represented by the flavonoid quercetin and the ethanol extracts of either green coffee bean or grape seed in prevention of PD in rats [1]. The research focused on the effects of nutraceuticals on iron status and the immune system and the proposed mechanisms for PD management. The expression of brain dopamine receptors D1 (DRD 1) and divalent metal transporter 1 (DMT 1) are among the mechanisms that have been studied. The study also followed the histopathological brain changes to confirm the biochemical and molecular changes.

The study claimed that PD pathogenesis might mainly originate as a result of alteration in the immune system, a hypothesis with which I agree. A debate was issued by the authors on whether the immune system is involved in the induction of PD, as cited by Kannarkat [2], or whether the disease itself, with an injured brain, might result in changes in the immune system. Neuronal damage in PD patients and damaged regions of the brain could result from the inflammation represented by increased cytokines along with high oxidative stress [2,3]. The results of the study showed elevated plasma tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) with a reduction in CD4 in the experimental PD, denoting a change in the immune system, but the study could not solve the aforementioned debate; however, both suggestions might be involved (i.e., alteration in the immune system might be a cause and a result of PD at the same time). Iron deficiency anemia (IDA) was demonstrated in the experimental model of PD in that research, a finding that supports the suggestion of the occurrence of IDA in PD patients. Iron deficiency anemia was emphasized by reduction in plasma iron, %transferrin saturation, and ferritin along with elevation of total iron binding capacity, soluble transferrin receptors (sTfR), and sTfR/log ferritin which are collectively considered as good biomarkers of anemia. The authors raised another explanation of brain neurodegeneration, which is the up-regulation of DMT1 in the experimental PD that induced the deposition of iron in the brain, thereby generating high oxidative stress and neuronal apoptosis in the brain [4]. The authors also assumed that IDA might partially be developed due to the deposition of iron in brain tissue in PD patients, resulting in changes in iron balance and homeostasis in the body.

The authors also discussed the interplay between immunity and iron status. The activation of the immune system can lead to a change in iron balance, which may inhibit erythropoiesis and contribute to the pathology of the immune system. Both acute-phase protein and cytokines might be important issues in the pathogenesis of IDA in PD because they lead to iron retention within macrophages and hypoferremia. On the other hand, there is a recent concept related to the role of iron in immunity. Iron proteins like ferritin and transferrin receptors influence innate immunity. In that study, soluble transferrin receptors were elevated, whereas ferritin was reduced in the experimental PD. Although ferritin as an acute phase reactant is expected to increase throughout inflammation, the presence of anemia may cancel this effect. The authors showed that iron loading and depletion can negatively affect the immune system. In that study, the neurotransmitter dopamine was shown to be decreased in experimental PD, as evidenced by the down-regulation of DRD1 that also inhibited neuronal growth.

The study showed improvement in iron status on the administration of the nutraceuticals, which was ascribed to an effect on the immune system represented by IFN-γ, TNF-α, and CD4, in addition to enhancement of the expression of brain DRD 1. The authors explained the neuroprotection by the nutraceuticals through the down-regulation of brain DMT1 that reduces iron deposition in the brain, which consequently resulted in the inhibition of oxidative stress and inflammation. The study showed that green coffee bean and grape seed extracts improved the reduced body weight gain in experimental PD, which has been ascribed to improved non-motor activity. The study also demonstrated improvement in brain histopathology by nutraceuticals,

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confirming the biochemical and molecular ameliorations. The study reported a higher content of flavonoids and phenolic compounds in green coffee beans compared to grape seeds. The improvement in experimental PD by green coffee beans was attributed to the presence of caffeine that could inhibit brain oxidative stress. It was reported that quercetin, but not caffeine, is the predominant neuroprotective flavonoid in coffee beans [5]. The study demonstrated that the bioactive compounds in coffee beans, including caffeine, chlorogenic acid, and quercetin, could have neuroprotective effects *via* reduction of IFN-γ and inflammatory cytokines like Interleukin-6 and TNF-α released from activated microglia and astrocytes. Quercetin was ascribed as being the major neuroprotective constituent in coffee in PD due to its strong antioxidant and anti-inflammatory activities towards brain cells [5]. Other bioactive compounds called β-carbolines' alkaloids were mentioned (but not determined) to be present in coffee beans and to have a protective effect towards PD through neuroprotective, antioxidant, and anti-inflammatory activities [6]. On the other hand, grape seed extract with its phenolic contents could improve experimental PD through antioxidant, anti-inflammatory, and immune-regulatory effects *via* suppressing presynaptic oxidative stress and inflammation [7]. The study ascribed the bioactivity of the grape seed extract to its content from flavonoids and three different flavan3-ols like catechin, epicatechin, epicatechin gallate, and its polymers, along with procyanidins and tannins.

The study suggested that the mechanism of action of the nutraceuticals as anti-Parkinsonian was attributed to their antioxidant, anti-inflammatory, and immune-regulatory effect and that they could reduce iron accumulation in the brain by downregulation of DMT1, thereby reducing brain cell injury. These effects could collectively exert anti-apoptotic activity in brain cells. The study also showed that such nutraceuticals could act as DRD1 agonists. The improvement in iron status in the experimental PD by nutraceuticals could be attributed to immune regulation and reduction of DMT1. It is worth mentioning that it would be very interesting if colonic microbiota was evaluated in that research due to its reported interrelation with the immune system and inflammatory condition.

Disclosure statement

No potential conflict of interest was reported by the author.

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