

The Effect of Antioxidants on Olfactory Dysfunction in Parkinson's Disease

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ABSTRACT

Parkinson's disease is one of the most prevalent diseases worldwide, with approximately 10 million people worldwide being affected in 2016³. Olfactory dysfunction is a common hallmark of early Parkinson's disease, and research indicates that antioxidants work against reactive oxygen species (ROS) in Parkinson's disease. Lewy bodies, alpha-synuclein protein aggregates, are the cause of the death of dopaminergic neurons in Parkinson's disease. Given olfactory dysfunction is one of the first symptoms of Parkinson's disease, it has intrigued many to discover its underlying importance. When Lewy bodies are found in the olfactory bulb, there was a greater than 90% correlation with the presence of Parkinson's disease¹⁷. It has been observed that alpha-synuclein aggregation may begin in the olfactory bulb before moving to other parts of the brain¹⁸. Free radicals, such as ROS, are related to dopamine such as oxidized dopamine, and can help sustain alpha-synuclein toxic forms^{13, 25, 26}, leading to aggregation. Therefore, antioxidants could play a substantial role in mediating the effects of ROS. This paper will review our current understanding of the usage of antioxidants in alleviating the symptoms posed by oxidative stress and what that could mean for Parkinson's disease models by providing a critique of 4 papers. Each paper will discuss the usage of treatment for olfactory dysfunction and the potential implications that follow the results. After, the paper will propose new studies to determine whether antioxidants are effective in diminishing the extent of olfactory dysfunction in patients with Parkinson's disease.

Introduction

Parkinson's Disease Symptoms

In Parkinson's disease, the death of dopaminergic neurons in the substantia nigra pars compacta causes a loss of dopamine in the basal ganglia, leading to the hallmark motor symptoms seen in patients with Parkinson's disease². This death of dopaminergic neurons is caused by protein aggregates of alpha-synuclein called Lewy bodies⁸. Parkinson's disease is identifiable through both motor and non-motor symptoms. Motor symptoms include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment². The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria^{2,4} states that a diagnosis can be made with bradykinesia, or "slowness of initiation of voluntary movement," and one or more of the following symptoms:

1. Muscular rigidity^{1, 2, 4}
2. 4-6 HZ rest tremor^{1, 2, 4}
3. "Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction"^{2, 4}

One of the symptoms for diagnosis, the resting tremor, has been linked to a loss of inhibition in the cerebellar thalamus due to a loss of dopamine⁶. One study found that, by injecting 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to kill dopaminergic neurons in marmoset primates, two out of the three marmosets

developed postural head tremors, while the other marmoset received a smaller dose of MPTP and showed fewer symptoms⁷, indicating that dopamine loss can cause not only many different types of tremors, but many different types of motor symptoms in different regions of the body.

While motor symptoms are more obvious, they emerge only after 60-80% of the dopamine in the striatum has been depleted. However, non-motor symptoms emerge earlier but often go unnoticed until after diagnosis^{1,7}. While discretely appearing earlier, these non-motor symptoms also get worse over time, especially the cognitive symptoms⁷. These early symptoms can consist of constipation, the acting out in dreams during rapid eye movement (REM) sleep, olfactory dysfunction, asymmetric upper shoulder pain, or depression¹. It was observed that the average time between the appearance of a symptom of Parkinson's disease and a diagnosis is around 10 years⁵, highlighting a clinical need to enhance earlier recognition and diagnosis.

Genetic Causes

The loss of dopaminergic neurons in PD is affected by two main factors: genetic and environmental factors, where genetic factors make up around 10-15% of the condition⁹. Parkin was the first gene identified to cause parkinsonism in an autosomal-recessive manner and has been correlated with early-onset Parkinson's disease^{8,11}. While the pathology of Parkin-linked disorders indicated a loss of dopaminergic neurons in the substantia nigra pars compacta, many cases do not have Lewy bodies^{8,11}. The most common known genetic cause of late-onset Parkinson's disease is a mutation in LRRK2. The protein LRRK2 is associated with the endoplasmic reticulum of dopaminergic neurons, and carriers for this mutation have Lewy bodies near the brainstem region^{8,10}.

Mutations in the SNCA gene, which codes for the protein alpha-synuclein, have been found to increase the risk of Parkinson's disease¹². However, alpha-synuclein has a predominant effect on Parkinson's disease patients through the formation of Lewy bodies. While not much is known about alpha-synuclein^{8,12}, it is known to play a role in the presynaptic terminal, particularly in membrane trafficking and cytoskeletal organization^{8,12-14}. Its depletion has been correlated with the loss of the amount of synaptic vesicles^{13,31}, indicating that it plays a role in maintaining the vesicles^{12,13,31}.

Alpha-synuclein aggregates due to many mechanisms, which are not all known in great detail. Dopamine is reactive, causing oxidation to produce reactive oxygen species (ROS). These ROS can interact with alpha-synuclein to make it easier to aggregate^{13,25,32,37}. Alpha-synuclein affects dopamine production by affecting tyrosine hydroxylase (TH), the enzyme that converts tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA)³². The overexpression of alpha-synuclein leads to less TH transcription, reducing the amount of dopamine^{32,33}. Silencing alpha-synuclein has been linked to the increased activity of TH³²⁻³⁴. Related to its known function, the overexpression of alpha-synuclein in hippocampal neurons has been linked to impaired exocytosis, causing dopamine to stay in the cell^{33,35,36}. Alpha-synuclein's regulation of dopamine transporter activity can also play a role in controlling dopamine levels^{13,15,32}. As dopamine can prevent the conversion of protofibrils to mature fibrils, its depletion in some cases can support aggregation³⁷. This indicates that alpha-synuclein overexpression decreases dopamine levels by decreasing both its production and activity. However, the specific role of alpha-synuclein in the mechanism of initiation of dysfunction in Parkinson's disease is also unclear.

Olfaction

Olfactory dysfunction is listed as an early non-motor symptom that has been linked to the speed and severity of Parkinson's disease¹⁶. The olfactory system is the system linked to the sense of smell, where olfactory receptors detect molecules causing action potentials²¹. When Lewy bodies are found in the olfactory bulb, there was a greater than 90% correlation with the presence of Parkinson's disease¹⁷. In addition, the alpha-synucleinopathy observed in the olfactory bulb was indicative of Lewy body formation in other areas, implying that olfactory

dysfunction can predict Lewy body formation in other areas¹⁷. It was particularly observed that alpha-synuclein aggregation may begin in the olfactory bulb area before moving to other parts of the brain¹⁸. The first areas where lesions appear are the olfactory bulb and anterior olfactory nucleus, where alpha-synucleinopathy spreads through neuronal connections¹⁹⁻²⁰. A study where fibrillar alpha-synuclein was injected into wild-type mice revealed that alpha-synuclein did spread from the olfactory bulb, similar to in the early stages of Parkinson's disease¹⁹. Not only does alpha-synuclein begin its path and spread from the olfactory bulb, but it is associated with being the reason for olfactory dysfunction^{19, 22}. Alpha-synuclein aggregation in the olfactory bulb was found to increase mitral/tufted cell firing directly and indirectly by inhibiting granular cells²². Therefore, olfactory dysfunction can serve as an early symptom^{1, 17} which can be used to alert patients of their risk of Parkinson's disease, through possible measures such as an olfactory bulb biopsy¹⁷. However, it is not known what causes alpha-synucleinopathy and why it occurs in the olfactory bulb¹⁸.

Antioxidants

Through reactions in the cell, byproducts known as reactive oxygen species (ROS) can be developed²³. Free radicals, defined by a chemical structure that contains an unpaired electron, are byproducts of reactions in the cells²³. ROS are a type of free radical. When there are more ROS, types of free radicals, than homeostatic levels, a process known as oxidative stress can occur damaging the cell^{23, 30}. However, antioxidants can prevent cell damage by giving up some of their electrons, neutralizing the effect of ROS²⁴, keeping homeostasis³⁰. As the free radicals related to dopamine such as oxidized dopamine help sustain alpha-synuclein toxic forms^{13, 25, 26}, it could lead to aggregation. However, the process of aggregation is of further study as it is unclear which forms, fibrillar¹³ or oligomeric²⁵ or both²⁶, lead to concrete aggregation as a result of oxidative stress by increasing synucleinopathy. A study in vivo, however, indicated that aggregation is supported by oxidative stress²⁷. As a result, current research is testing whether antioxidants can prevent aggregation. Flavonoid intake has been seen to have somewhat of a negative correlation with Parkinson's disease risk²⁸, while curcumin was found to reduce A53T alpha-synuclein cell death by reducing ROS²⁹. However, with all of these studies, a concrete analysis in reducing olfactory dysfunction through anti-oxidants, potentially slowing the onset of Parkinson's, has not been produced.

Critique of Previous Literature

In this section, a deeper look will be taken at four papers that deal with the topics of olfactory dysfunction in Parkinson's disease and the use of antioxidants/oxidative stress.

Paper 1: Neuroprotective Effect of Carnosine in The Olfactory Bulb After Vanadium Inhalation in A Mouse Model

In this paper by Colín-Barenque et al. (2018), the researchers sought to determine whether carnosine had a protective effect on mice that inhaled vanadium pentoxide. Vanadium pentoxide is a chemical known to cause oxidative stress in the olfactory bulb, particularly when inhaled. It causes toxic activity by decreasing dopamine levels in the olfactory bulb, leading to dysfunction. Carnosine is an antioxidant that displays scavenger properties and reduces the amount of reactive oxygen species(ROS). Previous studies have shown a partial benefit in improving the symptoms of Parkinson's disease. In this study, researchers hypothesized that mice who ingested carnosine with vanadium inhalation would have less damage than those who inhaled vanadium without carnosine ingestion.

The researchers split mice into four groups: one group of mice that inhaled vanadium once a week, one group that inhaled vanadium once a week and ingested carnosine daily, one group that ingested carnosine daily but did not inhale vanadium, and one group that inhaled saline daily as a control. In order to test the effect of carnosine on olfactory dysfunction caused by vanadium pentoxide, the researchers tested how long it took each group of mice to locate chocolate after exposure to the smell. The results indicated that the group that had inhaled vanadium alone took the longest to locate the pellet, while the other three groups, including the group that had vanadium and carnosine, took around the same time, which was significantly less than vanadium alone. Granule cell size in the olfactory bulb of mice exposed to only vanadium was smaller than the control, but with carnosine was similar to the control. In addition, the dendritic spine number of olfactory bulb neurons was lower after vanadium alone, but when vanadium was paired with carnosine, the spine number was similar to control. Furthermore, an ultrastructural examination indicated that cells exposed to vanadium alone had significantly more damaged organelles and more cells that had undergone apoptosis, compared to those that had vanadium plus carnosine. In addition, malondialdehyde (MDA), a predictor of oxidative stress, had increased after vanadium alone, but with vanadium plus carnosine, it was similar to control. The results that carnosine with vanadium had shown more dendritic spines and less organelle damage and apoptosis support the hypothesis that carnosine with vanadium will have less damage than just vanadium. This led to the conclusion that the scavenger properties of carnosine prevented the production of reactive oxygen species associated with vanadium inhalation. Vanadium exposure has been shown to mimic some of the symptoms of Parkinson's disease, and these results show that the antioxidant carnosine does have an impact on the effects of vanadium. Therefore, the main conclusion of the paper is that carnosine can prevent olfactory dysfunction caused by vanadium through its scavenger properties, and could potentially also be used to treat the symptoms of Parkinson's disease.

Paper 2: Empagliflozin Attenuates Neurodegeneration Through Antioxidant, Anti-Inflammatory, And Modulation of Alpha-Synuclein and Parkin Levels in Rotenone-Induced Parkinson's Disease in Rats

In this paper by Ahmed et al. (2022), Empagliflozin (EMP), a drug used for diabetes, was tested to see the effect on mice that have been exposed to rotenone (ROT). EMP is an antidiabetic drug that has anti-inflammatory and antioxidant properties, while ROT is a pesticide that, when administered, results in alpha-synuclein aggregation and selective dopaminergic neurodegeneration. In this study, four groups were present: a control group which was given dimethyl sulfoxide, a group given ROT, and two groups with different doses of EMP along with ROT.

The researchers first determined that EMP did not cause changes in blood glucose levels. They performed the open field test to measure the distance traveled and found that EMP treatment increased the number of squares crossed in comparison with the ROT-only mice. In the rotarod behavioral test, the mice were placed in a circular rod where the time on it was recorded to test coordination. It was indicated that the mice with ROT only had the least time, indicating the poorest coordination, while EMP treatment increased time on the rod, improving coordination. Thus EMP treatment improves motor deficits in locomotion and coordination in mice with ROT.

Furthermore, an analysis of different parameters related to oxidative stress indicated that EMP treatment decreased markers of oxidative stress present in ROT mice. This led the researchers to conclude that ROT increases oxidative stress and this is mitigated by the addition of EMP, especially in a significant dosage.

Dihydrophenyl acetic acid (DOPAC) and dopamine levels were significantly decreased following ROT administration. However, EMP administration with ROT increased these levels. This concludes that EMP can act to increase dopamine levels from the effects of ROT, which mimics Parkinsonian symptoms. After ROT, alpha-synuclein expression increased significantly, while EMP with ROT did not have such a significant increase, showing that EMP can be effective in slowing down the expression and, potentially, the aggregation

of alpha-synuclein. Therefore, the researchers were able to conclude that EMP can be effective not only in improving the motor symptoms of ROT administration in mice, but also in helping increase dopamine levels in addition to decreasing oxidative stress, implying a correlation between the two.

Paper 3: A Novel Mitochondrially-Targeted Apocynin Derivative Prevents Hyposmia and Loss of Motor Function in The Leucine-Rich Repeat Kinase 2 (LRRK2R1441G) Transgenic Mouse Model of Parkinson's Disease

Diapocynin has been shown to protect dopaminergic neurons after exposure to MPTP, and is closely related to mito-apocynin, a mitochondrially-based apocynin that increases permeability in the mitochondria cells. In this study by Dranka et al. (2014), the effect of mito-apocynin on LRRK transgenic mice that model Parkinson's disease was observed. The researchers hypothesized that the increased permeability of mito-apocynin would alleviate or help Parkinson's disease symptoms.

An open field test found that altering the LRRK gene did not significantly decrease the number of movements to squares when compared with control wild-type mice. However, the results indicated that there were more squares touched with LRRK mutant mice that received mito-apocynin compared to untreated LRRK mice. Using a Rotor Rod to test coordination, it was found that LRRK mice with mito-apocynin were likewise able to stay on the rod for longer than untreated mice. This indicated that the mito-apocynin helped alleviate some of the motor symptoms associated with mutation of the LRRK gene.

LRRK mice were also observed to have hyposmia. As a measure of olfactory function, the researchers compared the time it took for mito-apocynin-treated and untreated LRRK mice to locate two treats. They found that while the untreated LRRK mice took longer to identify the treats, LRRK mutant mice with mito-apocynin were able to find the treats in a shorter time, indicating that mito-apocynin can reduce the severity of hyposmia in LRRK mice.

The paper goes on to conclude that the mitochondria is a common location where reactive oxygen species are found and that mito-apocynin and diapocynin inhibit reactive oxygen species, which could be why both reduce the severity of some symptoms in Parkinson's models. The study concludes by stating that further research is necessary to determine the impact of oxidative stress on olfactory dysfunction.

Paper 4: Inhibition of Oxidative Stress in Cholinergic Projection Neurons Fully Rescues Aging-Associated Olfactory Circuit Degeneration in *Drosophila*

The research question for the study by Hussain et al. (2018), was to observe the effect of the reactive oxygen scavenger SOD2 on smell degeneration in aging flies. The researchers hypothesized that SOD2 in cholinergic projection neurons is necessary and sufficient to prevent smell degeneration in aging flies. In olfactory T-maze assays, smell performance on 8 odors declined with age in flies. The researchers first found that *Drosophila melanogaster* loses smell with age. SOD1 and 2 gene expression was also found to decrease with age. From this, the researchers found that getting rid of SOD2 in peripheral nerves reduced odor attraction and aversion. Therefore, it was identified as *Drosophila melanogaster*, proving that SOD2 is necessary for olfaction. Furthermore, it was shown that overexpression of SOD2 reversed the decline in flies, proving it is sufficient. This supported the conclusion that SOD2 is necessary and sufficient to prevent olfactory degeneration.

Critique Summary

These four papers demonstrate that the consumption of antioxidants in mice and *Drosophila melanogaster* can reduce olfactory dysfunction through a variety of factors. The study by Colín-Barenque et al. (2018) and

Hussain et al. (2018) shows that oxidative stress can cause olfactory dysfunction, while the study by Ahmed et al. (2022) shows that alpha-synuclein aggregation-induced dysfunction can be helped by anti-oxidants in mice. Finally, the study by Dranka et al. (2014) shows that antioxidants can reduce the severity of genetic-induced symptoms. Therefore, the papers show that antioxidants reduce the severity of symptoms by decreasing oxidative stress, which reduces not only its direct impacts but also those produced by downstream factors.

Future Directions

Gaps/Major Questions

In the previous two sections, antioxidants have been seen to be used in studies to see whether it would have an impact on a variety of factors in Parkinson's disease. However, there are some gaps in our understanding of the impact of antioxidants in olfactory dysfunction. Some of these major gaps are listed below, I will address some of these in the following section include:

1. While there have been multiple studies on the impact of antioxidants on olfactory dysfunction in animals such as mice and *Drosophila melanogaster*, there is no clear understanding of the impact of antioxidants on olfactory dysfunction in humans with Parkinson's disease (Critique).
 - a. There is also no understanding on if there is a certain point during the progression of Parkinson's disease where olfactory dysfunction is no longer curable.
2. There is no clear understanding of whether the impacts of oxidative stress are due to solely direct effects, solely through indirect activation of other damaging pathways, or a combination of both. While there have been a lot of causes for olfactory dysfunction identified, including alpha-synucleinopathy, the role and pathways through which oxidative stress affects olfactory function has not been quantified or clearly identified (Critique Paper 3).
3. There is no clear understanding as to whether using antioxidants in early stages of Parkinson's disease can prevent or slow down the progression of alpha-synucleinopathy in other areas such as the striatum.

The significance of these major questions is in the impact it can have in the treatment of diseases. If antioxidants do indeed slow down olfactory dysfunction, it can be used as an early treatment. If the magnitude of the impact that oxidative stress plays in olfactory dysfunction were known, it could help define the impact of other major components of olfactory dysfunction including alpha-synuclein. This could help provide not only a treatment for olfactory dysfunction, but also Parkinson's disease if it is seen to reduce the spread of alpha-synucleinopathy.

Hypothesis/Expected Outcomes

1. There will be an improvement in olfactory function after increasing the amount of antioxidants consumed in patients with Parkinson's disease. Because oxidative stress plays a major role in olfactory dysfunction, I would expect that using antioxidants can provide improvement.
 - a. Patients with Parkinson's disease that were diagnosed both recently and a long time ago will experience some recuperation.
 - b. Patients who have a family history of Parkinson's disease but are not currently diagnosed and who also experience olfactory dysfunction will show more recuperation than Parkinson's patients.
2. Taking antioxidants would prove to decrease/delay the spread of Parkinson's disease by decreasing the amount of Lewy bodies in multiple areas of the central nervous system.

Hypothesis 1 comes from the critique, where regardless of the source of Parkinsonian symptoms in animals (oxidative stress, genetics, alpha-synuclein aggregation), the administration of antioxidants alleviated the severity of the symptoms. Though some olfactory neurons will have already experienced cell damage, olfactory neurons regenerate³⁸. As antioxidants have been shown to decrease the aggregation of alpha-synuclein into toxic forms^{13, 25, 26, 32, 37}, they would be less likely to spread these forms to other neurons that regenerate. Additionally, ROS can alter the structure of alpha-synuclein to make it more likely to aggregate^{13, 25, 26, 32, 37}. Therefore, reducing the amount of ROS through anti-oxidants²⁴ would be able to make alpha-synuclein less likely to aggregate. Hypothesis 2 comes from the idea that the olfactory bulb is one of the first areas where Lewy bodies appear, and from there they then spread to the other regions of the brain¹⁷⁻²⁰. The reduction of Lewy bodies through antioxidants that would therefore lead to less Lewy bodies spreading and fewer Lewy bodies overall.

Methodology/Protocol

In order to test these hypotheses, the experiments designed require assessing different types of patients and observing the impact of antioxidants on each group. Along with that, as the impact of oxidative stress is uncertain, it would indicate that there would need to be a control group to understand the difference. With this, the experimental design would have to have multiple groups of people in different stages.

Experimental Groups

There will be three main categories of people that will be tested: people that have been diagnosed for Parkinson's disease within 1 year, people that have been diagnosed for Parkinson's disease more than 1 year ago, and people with family history that do not have a diagnosis, but experience olfactory dysfunction. Within each of these categories, there will be a group which will consume antioxidant supplements and a group that does not consume antioxidant supplements as a control. The antioxidant supplements will be a daily cup of blueberries, which has been known to have the strongest antioxidant capacity out of some berry fruits⁴². The amount of time this will continue will be based on the part of the study.

Experiment 1: Short-Term Experiment

All participants will come to a center where they will take the Sniffin' Sticks smell test, which is verified as reliable⁴⁰. Participants will have to determine a smell from four choices on a paper based on a stick's smell³⁹. Participants will do this 12 times for each stick³⁹. Similar to a multiple choice test, the number of correct answers will be tabulated where 10-12 correct answers indicate normal smell, 6-10 correct answers indicate hyposmia, while 0-6 correct answers indicate anosmia. While there are other tests, such as the University of Pennsylvania Smell Identification Test (UPSIT), Sniffin' Sticks is the most appropriate as participants may range from no motor deficits to severe motor deficits. Therefore, 12 questions would be more appropriate than the 40 questions of the UPSIT⁴¹. Participants will take this test before and after a 6 month period, where some of the experimental groups will add more antioxidants to their diet.

Experiment 2: Long-Term Experiment

While Experiment 1 may be able to show the impact of antioxidants on olfactory dysfunction, a long-term experiment can assess their long-term impacts. There are two main parts of the long-term experiment: two-year follow-up and lifetime. The two-year follow-up will be the same as Experiment 1, except that it will last for a 2-year period instead of 6 months. However, the life-time experiment is a little different. While there are some

ethical considerations that are necessary, a strong measure to see how big of an impact oxidative stress has on olfactory dysfunction would be through looking at the olfactory bulb after death. A previous study similarly used the Oxford-based OPTIMA brain bank to observe Lewy bodies in the olfactory bulb where 36.7% of the olfactory bulbs in dementia patients exhibited Lewy bodies⁴³. In the lifetime experiment, the number of Lewy bodies will be quantified in brain sections containing the olfactory bulb or the substantia nigra. The totals will be normalized by area analyzed to allow for comparison across samples to provide density measurements. By comparing the amount of Lewy bodies observed in the control group to the group that consumed antioxidants, not only would a determination be made on the impact of antioxidants on Lewy bodies, but also on the spread and amount of Lewy bodies in other areas. In fact, in order to observe whether olfactory dysfunction can be treated in late stages of Parkinson's disease, the different groups of people can be compared.

Hypothetical Results

If Hypothesis 1 is correct, those patients that take antioxidants will score better on the Sniffin' Sticks test than the control both on the 6-month short-term experiment, as well as on the 2-year long-term experiment. This would occur because of the combined fact that antioxidants prevent alpha-synuclein formation into toxic forms^{13, 25, 26, 32, 37} and because of neuroregeneration of olfactory neurons³⁸. Therefore, cells that regenerate would have less damage from ROS and from toxic forms of antioxidants. However, the hypothesis of whether patients in late stages could still be able to experience a less severe dysfunction would also be expected given that regeneration continues for life³⁸. If there is no difference between the experimental and control groups or if the experimental groups show more severe dysfunction than controls, then it would be concluded that the hypothesis was not supported. Similarly, if Hypothesis 2 is supported, it would be expected that patients that take antioxidants will have less Lewy bodies in the olfactory bulb and substantia nigra than the control. This would be expected to occur in all three groups of patients because less alpha-synuclein would be available to spread to the other regions¹⁷⁻²⁰. If there is no difference in the amount of Lewy bodies, then Hypothesis 2 would not be supported, indicating that antioxidants do not reduce the amount of Lewy bodies.

Conclusion

Antioxidants have been seen to reduce the severity of olfactory dysfunction in Parkinson's disease by decreasing alpha-synuclein aggregation into toxic forms, preventing cell death of dopaminergic neurons in the olfactory bulb. If in fact, antioxidants are able to be sufficient to decrease the severity of olfactory dysfunction in patients who have Parkinson's disease for a long time, this would provide evidence for antioxidants as a potential treatment for olfactory dysfunction. In addition, if antioxidants are found to support slowing the spread of alpha-synuclein by decreasing Lewy bodies in the substantia nigra, it would indicate that antioxidants could prove to be a treatment for broadly decreasing the spread of Parkinson's disease, which could impact multiple regions of the brain and associated symptoms, greatly increasing patient quality of life.

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