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Abstract
Oxidative stress is one of the underlying causes of Parkinson's disease (PD). Because of its antioxidant effect, we hypothesize that green tea consumption (3 cups daily for 3 months) would improve antioxidant status and reduces oxidative damage in Parkinson's disease. Fifteen subjects who were within the first five years of PD, on stable PD medication, and not regular green tea consumers were recruited. Iron status, oxidative stress and PD status were evaluated before and after 3 months of green tea consumption. Hemoglobin, serum iron, iron saturation and ferritin concentrations were used to assess iron status. Antioxidant enzymes including catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) were measured to determine antioxidant status. Lipid peroxidation and protein carbonyls were measured as oxidative damage markers. There were no changes in total motor scores of the Unified Parkinson's Disease Rating Scale (UPDRS), PDQ-39 total scores and various iron status markers after 3 months. Catalase ($p < 0.05$) and SOD activities ($p < 0.005$) were increased significantly indicating an improvement of antioxidant status. Both lipid peroxidation and protein carbonyls decreased by ~52% ($p < 0.01$) with green tea consumption, indicating less oxidative stress. In conclusion, 3 cups of green tea consumption for 3 months can improve antioxidant status and reduce oxidative damage in PD patients. Further studies are needed to determine if these changes result in slowing the disease progression.

Keywords
Parkinson's Disease, Antioxidant Enzymes, Oxidative Stress, Green Tea

Disciplines
Food Science | Human and Clinical Nutrition | Musculoskeletal Diseases | Nervous System Diseases

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Green Tea Consumption Reduces Oxidative Stress in Parkinson's Disease Patients

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Abstract

Oxidative stress is one of the underlying causes of Parkinson's disease (PD). Because of its antioxidant effect, we hypothesize that green tea consumption (3 cups daily for 3 months) would improve antioxidant status and reduces oxidative damage in Parkinson's disease. Fifteen subjects who were within the first five years of PD, on stable PD medication, and not regular green tea consumers were recruited. Iron status, oxidative stress and PD status were evaluated before and after 3 months of green tea consumption. Hemoglobin, serum iron, iron saturation and ferritin concentrations were used to assess iron status. Antioxidant enzymes including catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) were measured to determine antioxidant status. Lipid peroxidation and protein carbonyls were measured as oxidative damage markers. There were no changes in total motor scores of the Unified Parkinson's Disease Rating Scale (UPDRS), PDQ-39 total scores and various iron status markers after 3 months. Catalase ($p < 0.05$) and SOD activities ($p < 0.005$) were increased significantly indicating an improvement of antioxidant status. Both lipid peroxidation and protein carbonyls decreased by ~52% ($p < 0.01$) with green tea consumption, indicating less oxidative stress. In conclusion, 3 cups of green tea consumption for 3 months can improve antioxidant status and reduce oxidative damage in PD patients. Further studies are needed to determine if these changes result in slowing the disease progression.

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1. Introduction

Parkinson's disease (PD) is a slowly progressive, and neurodegenerative disorder. Several factors, such as aging,

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genetics, environment, oxidative stress, and inflammation, are involved in PD risk and progression. Among these factors, oxidative stress is critical in initiating and promoting neurodegeneration [1] [2]. Excess iron accumulation in the brain leads to free radical formation via the Fenton reaction, contributing to oxidation damage of lipids and protein and promoting cell death [3]. Significant elevation of iron has been reported in the substantia nigra of PD patients compared with age-matched controls [4] [5], indicating the critical role of iron in PD progression.

Antioxidants via improving the antioxidant defense system offer a promising approach to protect neuronal cells by removing free radicals, scavenging reactive oxygen species (ROS) or their precursors, maintaining redox homeostasis, and decreasing oxidative damage [6]. The antioxidant defense system can be enhanced exogenously by ascorbic acid, lipoic acids, polyphenols, and carotenoids, or endogenously by catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx). Beneficial effects of antioxidants in reducing oxidative stress in neuronal damage have been shown in many cell culture models [7]-[10]. *In vivo*, higher levels of antioxidants are required to result in protective effects on the central nervous system (CNS), which is extremely sensitive to redox changes and oxidative homeostasis due to the high level of oxidative metabolism [11]. Several studies have indicated that increased oxidative damage and reduced antioxidant activities may be responsible for the onset and progression of PD [12]-[14]. Therefore, the activation of antioxidant enzymes is one of the strategies to counteract the detrimental effects of ROS and restore the normal cellular redox balance [15].

Many antioxidants such as vitamin E, vitamin C, carotenoids, and flavonoids can improve antioxidant status, thereby decreasing oxidative stress [16]-[18]. Iron chelators, such as desferrioxamine (DFO), have shown neuroprotective effects in *in vitro* and *in vivo* studies [19] [20]. However, the side effects of DFO limit its usefulness. Catechin polyphenols can act as antioxidants by scavenging free radicals and chelating excess metal ions [21] [22]. They may also indirectly reduce oxidative stress, inhibiting redox-sensitive transcription factors, nuclear factor-κB, and pro-oxidant enzymes, such as inducible nitric oxide synthase, and inducing phase II antioxidant enzymes, such as glutathione S-transferases and SOD. (-)-Epigallocatechin-3-Gallate (EGCG) is the most abundant polyphenol in green tea that can bind iron [23]. It has been shown to have antioxidant effects *in vitro* by trapping peroxyl radicals, inhibiting lipid peroxidation, and contributing to the neuroprotective effect in several PD cell models [24]. EGCG can better represent the antioxidant function of green tea *in vivo*, due to its bioavailability and metabolism [25]. Epidemiological studies have shown that tea consumption is associated with lower prevalence of PD; however, data showing direct consumption of green tea for PD are limited. The purpose of this study is to identify the beneficial effect of green tea consumption in PD patients. We hypothesized that green tea consumption in PD patients would improve clinical symptoms of the disease, and antioxidant status, and reduce oxidative damage to lipids and proteins.

2. Methods

2.1. Study Design and Participants

Patients (n = 15; 9 males, 6 females) were recruited from the Parkinson's Disease and Movement Disorder Center at the University of Kansas Medical Center (KUMC). The protocol was approved by the Institutional Review Board of KUMC, as well as Iowa State University. All patients provided written informed consent. The inclusion criteria included patients within the first five years of PD diagnosis, on a stable PD medication regimen, with no anticipated changes in medication throughout the study, age between 50 to 80 years, and willing to drink 3 cups of green tea daily for 3 months. The exclusion criteria included premenopausal women, atypical parkinsonism or parkinsonism resulting from other causes including toxicity, drugs and head trauma, and patients with uncontrolled chronic diseases, smokers, and current green tea drinkers (≥3 cups/day). Subjects were provided with tea bags (Lipton® 100% Natural Green Tea) and requested to drink 3 cups of green tea per day every day for 3 months. Patients were instructed to steep one green tea bag in one cup of boiling water for 4 minutes. Height and weight of each subject was measured using a balance beam scale.

2.2. Assessment of PD Status

At baseline and at the 3-month visit, the Unified Parkinson's Disease Rating Scale (UPDRS), as well as Hoehn & Yahr Staging (H & Y) and the Schwab and England Activities of Daily Living Scale (S & E) were completed to assess the PD-related disability. The 39-item Parkinson's Disease Questionnaire (PDQ-39) was used to assess quality of life. Various other measures were used to evaluate PD non-motor symptoms, such as depression

(Beck Depression Inventory), anxiety (Beck Anxiety Inventory), sleepiness (Epworth Sleepiness Scale), mental status (Mini Mental State Examination) and fatigue (Fatigue Severity Scale).

2.3. Blood Analysis

Venous blood samples were drawn at baseline and the 3-month visits. Both serum and plasma were collected in tubes containing no anticoagulant and EDTA, respectively for analysis. Erythrocytes were collected after the plasma was separated from the whole blood; red cells were mixed with four volumes of HPLC grade water and centrifuged for 15 min at 4˚C. Supernatant was frozen in aliquots at −80˚C until use for measuring antioxidant enzymes. The antioxidant enzyme activities in erythrocytes, including catalase, SOD, and GPx were determined by using commercial assay kits (Cayman Chemical Company, Ann Arbor, MI, USA). Serum malondialdehyde (MDA) concentration was estimated by thiobarbituric acid reactive substances (TBARS) assay to determine lipid peroxidation. Protein carbonyls in plasma were measured by using commercial kits (Cayman Chemical Laboratories, Houston, TX, USA). Iron status was measured as serum ferritin with RIA kit (Ramco Laboratories, Houston, TX, USA). Hemoglobin, iron saturation and serum iron were determined by the certified clinical laboratory (Lab Crop, Kansas City, MO, USA).

2.4. Statistical Analysis

Wilcoxon matched paired t-tests were used to compare the changes in PD rating scales and student t-tests were used to compare the changes in antioxidant enzymes, TBARS, protein carbonyls, and iron status between baseline and post-intervention. The mean differences between baseline and 3 months post-intervention were considered significant at $p \leq 0.05$.

3. Results

3.1. Subject Description

A total of 15 subjects were included in the study. One subject was withdrawn during the study period due to noncompliance with tea drinking, therefore, data are provided for 14 subjects. The median age of the14 subjects was 61 years with a range of 51 to 79 years. Median BMI at baseline was 28.2 kg/m^2 (overweight) with a BMI range of 18 kg/m^2 to 41.8 kg/m^2. No significant changes in BMI occurred over the 3 months. At 3 months, median BMI was 28.6 kg/m^2 (overweight) with a range of 18.5 kg/m^2 to 45.6 kg/m^2. Based on adult BMI cut-off values, subjects were classified as obese (n = 6, BMI ≥ 30 kg/m^2), overweight (n = 6, BMI 25.0 - 29.9 kg/m^2), healthy (n = 1, BMI 18.5 - 24.9 kg/m^2), and underweight (n = 1, BMI < 18.5 kg/m^2).

3.2. Clinical Outcomes

Clinical outcomes are shown in **Table 1**. There were no significant changes in total UPDRS and total PDQ-39 scores after 3 months of green tea consumption compared to baseline suggesting no changes in PD symptoms. There were no adverse effects reported during the study.

3.3. Changes in Iron Status

Details of iron status are shown in **Table 2**. None of the subjects showed anemia since the mean hemoglobin was in the normal range (14.3 g/dL). The iron status indicators such as serum iron and transferrin saturation were also in the normal range according to the cut off values provided by the clinical lab. The average serum ferritin was 51.9 ng/mL with a range of 4.2 to 160.3 ng/mL, indicating normal iron status. No significant changes were found in hemoglobin, serum iron, iron saturation, or serum ferritin from baseline to 3-months. Overall, iron status was not affected by green tea consumption.

3.4. Changes in Antioxidant Enzymes

Compared to baseline, the mean activity of SOD in erythrocytes increased by 37% ($p = 0.0025$) (**Figure 1(a)**) at 3-months. Similarly, mean catalase activity increased by 28% ($p = 0.0483$) (**Figure 1(b)**). Although there was a 13% increase in the mean activity of GPx after green tea consumption, the change was not statistically significant ($p > 0.05$) (**Figure 1(c)**). Overall, antioxidant enzyme activities were improved following green tea consumption.

Table 1. PD rating scales in subjects at baseline and after 3 months of green tea consumption.

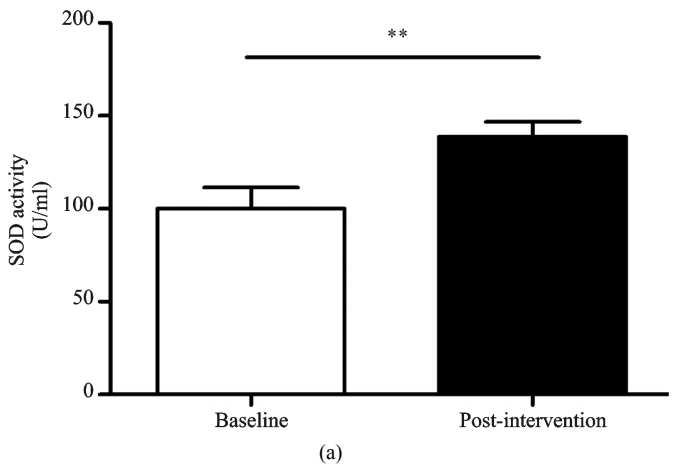
Ion Assessment	Mean (SD) Range	
	Baseline	3 Months
PDQ-39		
PDQ Total Score	16.4 (11.5) 2.6 - 42.9	19.6 (18.4) 0.64 - 44.4
UPDRS		
Mentation, Mood, and Behavior	0.7 (1.2) 0 - 4	1.1 (1.6) 0 - 5
Activities of Daily Living*	9.2 (5.7) 0 - 22	9.9(5.7) 1 - 22
Motor Examination*	21.2 (7.5) 8 - 38	18.1 (9.2) 6 - 38
Total Score	31.1 (12.6) 8 - 58	29 (15) 7 - 65
Beck Depression Inventory	7.1 (5.8) 0 - 21	7.9 (7.9) 0 - 24
Beck anxiety inventory	10.3 (6.7) 1 - 20	9.3(7.8) 0 - 13
Epworth Sleepiness Scale	7.8(4.4) 3 - 17	7.7(5.1) 4 - 16
Mini Mental State Examination (MMSE)*	29.5 (0.7) 28 - 30	29.9 (0.4) 29 - 30
Fatigue Severity Scale	28.4 (13.0) 13 - 55	32.1 (14.3) 12 - 55

Values are mean ± (SD) and range, n = 14. *$p < 0.05$.

Table 2. Subject description and iron status at baseline and after 3 months green tea consumption*.

	Height (M)	Weight (kg)		BMI (kg/M^2)		Hemoglobin (g/dL)		Serum Iron (μg/dL)		Iron Saturation (%)		Serum Ferritin (ng/mL)	
		B	P	B	P	B	P	B	P	B	P	B	P
Mean ± (SD)	1.7 (0.1)	87 (20.5)	87.5 (22.5)	28.9 (6.0)	29.1 (6.7)	14.3 (1.5)	14.2 (1.5)	85.9 (28.5)	87.5 (38.2)	25.1 (8.7)	26.5 (12.6)	51.9 (4.2 - 160.3)	50.9 (4.8 - 172.9)

*Mean ± (SD), n = 14. B, baseline; P, post-intervention. Values of serum ferritin were median with ranges due to non-normal distribution. No significant changes were found in hemoglobin, serum iron, iron saturation and serum ferritin at baseline and post-intervention.



(a)

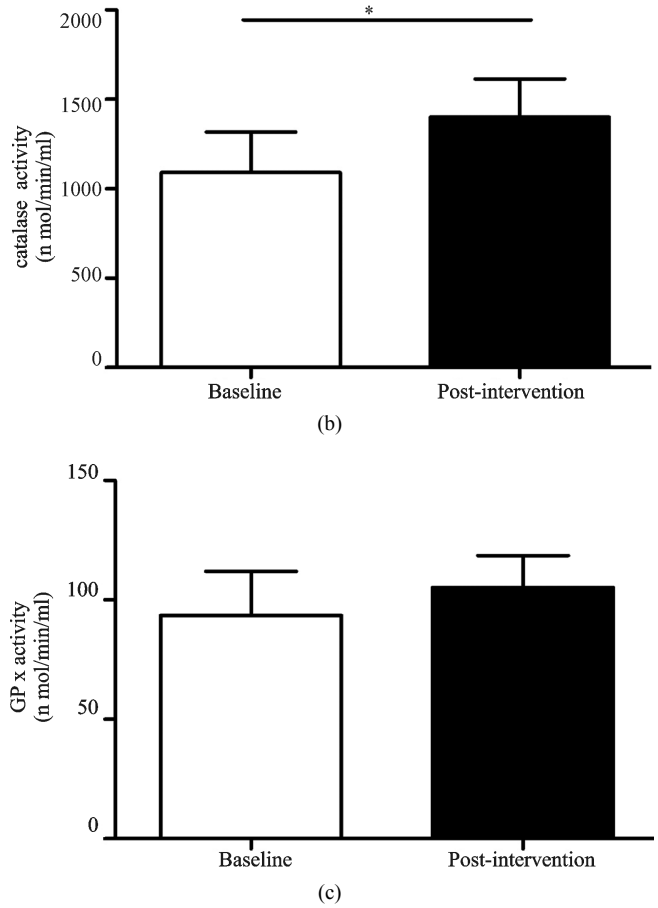


Figure 1. Antioxidant enzyme activities in erythrocytes at baseline and after 3-month green tea consumption (a) SOD, (b) catalase, and (c) glutathione peroxidase (GPx). Values are mean ±SD, n=14. $^{*}p < 0.05$; $^{**}p < 0.01$.

3.5. Changes in Oxidative Damages

The mean MDA concentration decreased significantly ($p < 0.01$) from 2.5 ± 0.9 to 1.2 ± 0.8 μM after green tea consumption (**Figure 2(a)**), suggesting adecrease in lipid peroxidation. Protein carbonyl concentrationalso decreased significantly ($p < 0.01$) from 0.82 ± 0.21 to 0.39 ± 0.27 nmol/mg (**Figure 2(b)**), suggesting a decrease in protein damage.

4. Discussion

Iron plays a critical role in CNS functioning and is closely related to the progression of neurodegenerative diseases [26]. Excess iron, especially non-transferrin bound iron, can induce ROS generation and cause oxidative damage. Significantly higher amounts of iron have been reported in PD brains compared with age-matched controls [5] [27]. On the other hand, low circulating iron levels have also been reported in PD [28], suggesting iron deficiency or problems with iron mobilization from tissues such as liver and brain, possibly contributing to PD progression. Other research has shown no change in serum iron levels, but a significantly higher level of iron in cerebrospinal fluid in PD patients, compared with healthy controls [29]. In our study, iron status values at baseline were in the normal range and none of them indicated iron deficiency anemia or iron excess. Although there is a concern that polyphenols in the green tea can inhibit iron absorption and alter overall iron status, no changes in iron status after 3 months of green tea consumption were observed in our study. Our iron status results are similar to those reported previously [30]. Therefore, the iron relocation within specific regions in the brain might become an important issue to trigger the progression of PD rather than affecting overall body iron status.

Oxidative stress can cause dopaminergic cell death and neurodegeneration. Increased oxidative stress and de-

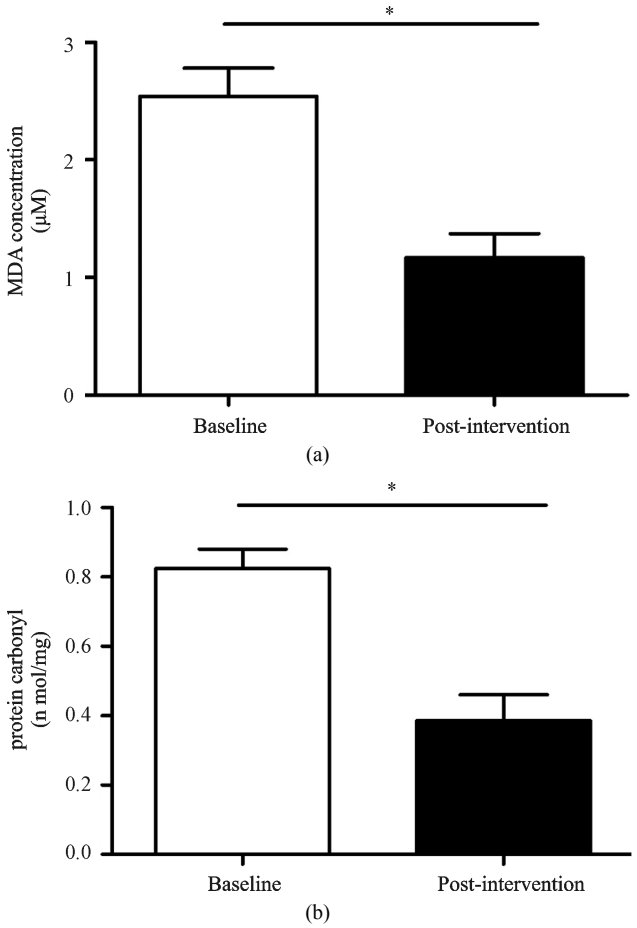


Figure 2. Lipid peroxidation (a), measured as MDA concentrations in serum (μM) and protein damage (b), measured as protein carbonyl concentration in plasma (nmol/mg protein) at baseline and after 3-month green consumption. Values are mean ±SD, n = 14. $^{*}p < 0.01$.

creased antioxidant enzymes have been shown in several studies with PD patients [12] [31] [32]. Since PD is also related to high iron accumulation in the brain, the abnormal iron metabolism may be attributed to oxidative stress. Therefore, maintaining normal iron homeostasis and enhancing antioxidant status may be one of the strategies to slow down or prevent PD. Green tea poly phenols have been shown to be beneficial not only for neurological diseases, but also for cancer and inflammatory processes [33]-[35]. EGCG is the main catechin component, contributing to the beneficial effects of green tea due to its iron chelation, antioxidant, and anti-inflammation capabilities [36]. EGCG has been shown to protect neurotoxin-induced dopaminergic cell death in both *in vitro* and *in vivo* models [37] [38]. EGCG is also found to enhance the activities of antioxidant enzymes, catalase, and SOD in the striatum of mice in a neurotoxin induced PD model [39]. Our results showing the improvement of antioxidant status with green tea support previous studies with PD patients. Although iron status remained unaltered, there was a significant increase in catalase and SOD activity and a decrease in oxidative damage in lipids and proteins, suggesting that green tea poly phenols could potentially be used as therapeutic supplements. We believe that the beneficial effects are due to green tea consumption since patients did not change their medication use during the study and there is no indication of changes in dietary consumption (based on personal communications). No adverse effects for consuming green tea for 3 months suggesting the safety of its use in PD patients.

Although epidemiological studies have shown a negative correlation between green tea consumption and the risk of neurological disorders including PD [40] [41], limited human data are available with green tea intervention. A cross-sectional study reported an inverse relationship between green tea consumption and cognitive impairment, but not cognitive decline. This may be due to the small sample size in that study [40]. In our study,

patients were not cognitively impaired according to the MMSE, therefore we could not draw any conclusions on the relationship between green tea and cognitive changes. Chan (2009) showed that green tea polyphenol (0.4 g, 0.8 g, and 1.2 g daily) in early PD patients over a span of 6 months improved UPDRS scores [42]. In our study, participants consumed 3 cups of green tea containing approximately 550 mg total polyphenols (unpublished results) daily for 3 months, which was the lower end of the dose in the previous study, and showed no effect on the total UPDRS scores. Although we were not able to conclude that green tea reduce the PD symptoms, our results showing improvement in antioxidant status and reduced oxidative damage in PD patients after the 3-month intervention are promising.

There are multiple limitations in our study. One of the limitations of our study was the lack of an age-matched control group of PD patients who did not consume green tea, as well as not monitoring compliance in consuming green tea. However, our data with 3 randomly selected subjects showed higher levels of total polyphenols in the plasma suggesting compliance in consuming tea (data not shown). Our data indicated no change in total UPDRS scores, total PDQ-39 scores, or PD non-motor symptom measures, *i.e.*, BDI and BAI, following 3 months of green tea consumption, but our study was limited by the small sample size and a short follow-up duration, which did not allow for observation of potential clinical benefits of green tea. While we used a realistic dietary approach to green tea consumption, using a purified EGCG supplement might be more useful for determining the beneficial effects on PD patients in a future clinical study.

Although our study had limitations, it also had several strengths. Our 3-month green tea intervention significantly improved antioxidant status and reduced oxidative damage in early PD patients without affecting their iron status. Based on this pilot study, a future study including a large number of subjects, the use of an EGCG supplement possibly along with a treatment regimen, and an age-matched control group will be useful to clarify the effect of EGCG on the clinical symptoms and progression of PD.

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