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Original Research

The Effectiveness of Coffee Cherry Extract as a Neuroprotector in High-Fat Diet and Streptozotocin-Induced Diabetic Rats with Cognitive Impairment

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Background: Diabetes mellitus causes chronic hyperglycemia that induces inflammation and neuronal damage, leading to cognitive impairment. Coffee cherry contains bioactive compounds (polypehenols, flavonoids, caffeine, chlorogenic acid) with neuroprotective potential. **Objective:** To evaluate the effect of coffee cherry extract on cognitive function and brain-derived neurotrophic factor (BDNF) in diabetic rats induced by high-fat diet (HFD) and streptozotocin (STZ). **Methods:** A post-test only control group design was applied using 24 male Wistar rats divided into six groups: normal control, STZ, HFD+STZ, HFD+STZ+metformin 200 mg/kgBW, HFD+STZ+coffee cherry extract 100 mg/kgBW, and HFD+STZ+coffee cherry extract 200 mg/kgBW. Parameters measured included spatial memory (Y-maze) and brain BDNF (ELISA). Data were analyzed using ANOVA and post hoc tests, with $p<0.05$ considered significant. **Results:** Coffee cherry extract at doses of 100 and 200 mg/kgBW significantly reduced blood glucose levels ($p<0.05$), increased the percentage of alternation in the Y-maze, and elevated BDNF levels compared to the HFD+STZ group. The best effect was observed at a dose of 200 mg/kgBW, which was comparable to or even better than metformin in several parameters. **Conclusion:** Coffee cherry extract is effective as a neuroprotector by improving spatial memory and increasing BDNF, thereby enhancing cognitive function in diabetic rats.

Keywords: BDNF, coffee cherry, cognitive impairment, neuroprotective.

INTRODUCTION

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Diabetes mellitus is a major global health problem with a prevalence that continues to rise each year.[1] Chronic hyperglycemia in diabetes not only leads to metabolic disturbances and vascular complications but also contributes to cognitive impairment.[2,3] Previous studies have demonstrated that insulin resistance and hyperglycemia trigger inflammation and mitochondrial dysfunction, ultimately resulting in neuronal damage and memory deficits.[3,4,5,6] Consequently, individuals with diabetes are more susceptible to cognitive decline and dementia.[7]

One of the key mechanisms underlying cognitive decline is the reduction of brain-derived neurotrophic factor (BDNF) expression. BDNF plays a crucial role in supporting neuroplasticity, neuronal growth, and survival. Decreased BDNF levels in diabetic conditions have been associated with memory impairment and an increased risk of neurodegenerative diseases such as Alzheimer's disease.[8,9,10,11] Furthermore, hyperglycemia accelerates the formation of reactive oxygen species (ROS), leading to neuronal damage.[5,12]

Efforts to prevent cognitive complications in diabetes can be approached pharmacologically or through natural products with neuroprotective effects. Coffee cherry extract, an agricultural by-product, represents a potential source as it is rich in polyphenols, flavonoids, caffeine, and chlorogenic acid.[13,14] These bioactive compounds have been reported to exhibit anti-inflammatory activities, as well as the ability to enhance BDNF expression, thereby potentially reducing and improving cognitive function.[10,11,15,16] Studies have shown that coffee cherry extract at a single dose of 100 mg significantly increases BDNF levels and improves neurofunctional performance in older adults with mild cognitive decline.[10] Additionally, regular coffee consumption is associated with slower cognitive decline through inhibition of brain β-amyloid accumulation and amelioration of neurotoxicity.[16]

However, scientific evidence regarding the effectiveness of coffee cherry extract as a neuroprotective agent in diabetes remains limited, particularly in animal models induced with high-fat diet (HFD) and streptozotocin (STZ). Most previous studies have focused on coffee bean extract or were conducted in non-diabetic models, even though the diabetic cognitive impairment model is clinically relevant to "type 3 diabetes" or sporadic Alzheimer's disease associated with insulin resistance.[5,6,12]

Therefore, this study was conducted to evaluate the effectiveness of coffee cherry extract in increasing BDNF levels and improving cognitive function in diabetic rats induced with HFD and STZ.

METHOD

This experimental study employed a posttest-only control group design using male Wistar rats (175–200 g, >3 months old). Twenty-four rats were randomized into

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six groups (n = 4 per group: normal control, STZ (30 mg/kgBW i.p.), STZ + high-fat diet, STZ + high-fat diet + metformin (200 mg/kgBW), STZ + high-fat diet + coffee cherry extract (100 mg/kgBW), and STZ + high-fat diet + coffee cherry extract (200 mg/kgBW).

Coffee cherry extract was prepared by maceration with 70% ethanol. The extract was administered orally via gavage once daily for 28 consecutive days. Diabetes was induced by STZ injection combined with a high-fat diet. Spatial memory was assessed using the Y-maze test (percentage of spontaneous alternation), while brain-derived neurotrophic factor (BDNF) levels were measured from brain tissue using ELISA.

Data were analyzed with normality testing. One-way ANOVA was applied for normally distributed data and Kruskal–Wallis for non-parametric data, followed by post-hoc tests. Statistical analysis was performed using SPSS, with significance set at $p<0.05$.

RESULTS

Blood Glucose Levels

The study was conducted after obtaining ethical approval from the Ethics Committee of FK UMSU (No. 1322.SP.01/KEPK/FKUMSU/2024). Blood glucose levels were measured from the tail vein of male Wistar rats (*Rattus norvegicus* sp.) in each group.

Table 1. Blood Glucose Levels in Male Wistar Rats with Cognitive Impairment After Coffee Cherry Extract Administration

Group	N	Mean (mg/dL)	Std. Deviation
Group 1	4	108.25	15.88
Group 2	4	195.25	13.05
Group 3	4	254.75	7.41
Group 4	4	130.50	11.00
Group 5	4	126.25	11.50
Group 6	4	128.00	2.16

Group 1: normal rats; Group 2: STZ-induced rats; Group 3: STZ-induced + high-fat diet rats; Group 4: metformin 200 mg/kgBW/day/oral; Group 5: coffee cherry extract 100 mg/kgBW/day/oral; Group 6: coffee cherry extract 200 mg/kgBW/day/oral

The highest mean glucose level was observed in group 3 (254.75 ± 7.41 mg/dL), representing severe hyperglycemia, whereas group 1 showed the lowest level (108.25 ± 15.88 mg/dL), which was close to normal. Group 2 also demonstrated an elevated glucose level (195.25 ± 13.05 mg/dL), indicating successful induction of diabetes. In contrast, the treatment groups (groups 4, 5, and 6) showed a reduction in blood glucose levels approaching normal values, with group 6 (128.00 ± 2.16 mg/dL) displaying the most stable result, suggesting it provided the most optimal effect in lowering blood glucose levels.

Normality testing confirmed that the data were normally distributed ($p > 0.05$). One-way ANOVA analysis revealed significant differences among groups ($p = 0.000$). Post hoc Tukey HSD analysis showed that group

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3 was significantly different from all other groups ($p < 0.05$). Group 1 was significantly different from the diabetic groups (groups 2 and 3) but not from the treatment groups (groups 4, 5, and 6). These findings indicate that treatment in groups 4, 5, and 6 effectively reduced blood glucose levels to near-normal values.

Spatial Memory

The Y-maze test was performed to assess spatial memory by observing rat activity in a Y-shaped maze and calculating the percentage of alternation.

Table 2. Spatial Memory (Y-Maze Alternation Percentage) in Male Wistar Rats with Cognitive Impairment

Group	N	Mean (%)	Std. Deviation
Group 1	3	64.40	9.53
Group 2	4	64.09	6.49
Group 3	4	61.39	15.85
Group 4	3	86.67	6.26
Group 5	4	92.52	5.31
Group 6	3	96.02	3.52

Group 1: normal rats; Group 2: STZ-induced rats; Group 3: STZ-induced + high-fat diet rats; Group 4: metformin 200 mg/kgBW/day/oral; Group 5: coffee cherry extract 100 mg/kgBW/day/oral; Group 6: coffee cherry extract 200 mg/kgBW/day/oral

***Note:** One rat in groups 1, 4, and 6 was excluded from Y-maze analysis due to failure to explore all three arms during the test. *

Groups 2 (64.09 ± 6.49%) and 3 (61.39 ± 15.85%) exhibited a reduction in alternation compared to the control group (64.40 ± 9.53%). In contrast, the treatment groups demonstrated a gradual increase, with group 6 achieving the highest alternation score (96.02 ± 3.52%) along with the lowest standard deviation, indicating that this treatment was not only effective but also consistent in improving the condition of the animal model.

Table 3. Post Hoc Tukey HSD Results for Spatial Memory

Group Comparison	Mean Difference (I-J)	Sig. (p-value)
Group 1 vs Group 2	5.31083	0.970
Group 1 vs Group 3	8.01583	0.853
Group 1 vs Group 4	-10.12667	0.749
Group 1 vs Group 5	-23.11417*	0.044
Group 1 vs Group 6	-26.62000*	0.027
Group 2 vs Group 3	2.70500	0.998
Group 2 vs Group 4	-15.43750	0.287
Group 2 vs Group 5	-28.42500*	0.006
Group 2 vs Group 6	-31.93083*	0.004
Group 3 vs Group 4	-18.14250	0.156
Group 3 vs Group 5	-31.13000*	0.003
Group 3 vs Group 6	-34.63583*	0.002
Group 4 vs Group 5	-12.98750	0.459
Group 4 vs Group 6	-16.49333	0.288
Group 5 vs Group 6	-3.50583	0.995

Significant at $p < 0.05$

Tukey HSD post hoc analysis revealed that groups 5 and 6 showed significantly higher alternation percentages compared with the

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diabetic groups (groups 2 and 3) ($p < 0.05$), while group 4 did not show a significant difference. Group 4 was in an intermediate position, showing an increasing trend but not yet significant, indicating relatively stable physiological conditions. These results suggest that the treatments in groups 5 and 6 exert stronger neuroprotective effects in improving cognitive impairment. Thus, coffee cherry extract has been shown to improve cognitive function in rats.

BDNF Levels

BDNF levels were measured from brain tissue of male Wistar rats (*Rattus norvegicus* sp.) in each group.

Table 4. BDNF Levels in Male Wistar Rats with Cognitive Impairment

Group	N	Mean (pg/mL)	Std. Deviation
Group 1	4	0.106	0.008
Group 2	4	0.057	0.022
Group 3	4	0.033	0.005
Group 4	4	0.156	0.229
Group 5	4	0.478	0.017
Group 6	4	0.715	0.013

Group 1: normal rats; Group 2: STZ-induced rats; Group 3: STZ-induced + high-fat diet rats; Group 4: metformin 200 mg/kgBW/day/oral; Group 5: coffee cherry extract 100 mg/kgBW/day/oral; Group 6: coffee cherry extract 200 mg/kgBW/day/oral

The diabetic groups showed decreased BDNF expression, with the lowest value observed in group 3 (0.033 ± 0.005 pg/mL). Conversely, the treatment groups (groups 4, 5, and 6) displayed a progressive increase in BDNF levels, with group 6 reaching the highest concentration (0.715 ± 0.013 pg/mL) along with the smallest variation, indicating that the treatment in group 6 had the most optimal and consistent effect in increasing BDNF levels.

Table 5. Post Hoc Tukey HSD Results for BDNF Levels

Group Comparison	Mean Difference (I-J)	Sig. (p-value)
Group 1 vs Group 2	0.0490250*	0.001
Group 1 vs Group 3	0.0730250*	0.000
Group 1 vs Group 4	-0.0499750*	0.001
Group 1 vs Group 5	-0.3712250*	0.000
Group 1 vs Group 6	-0.6087250*	0.000
Group 2 vs Group 3	0.0240000	0.169
Group 2 vs Group 4	-0.0990000*	0.000
Group 2 vs Group 5	-0.4202500*	0.000
Group 2 vs Group 6	-0.6577500*	0.000
Group 3 vs Group 4	-0.1230000*	0.000
Group 3 vs Group 5	-0.4442500*	0.000
Group 3 vs Group 6	-0.6817500*	0.000
Group 4 vs Group 5	-0.3212500*	0.000
Group 4 vs Group 6	-0.5587500*	0.000
Group 5 vs Group 6	-0.2375000*	0.000

Significant at $p < 0.05$

Post hoc Tukey HSD analysis demonstrated significant differences among almost all groups ($p < 0.05$), except between groups 2 and 3 ($p = 0.169$), meaning the mean values

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of groups 2 and 3 were relatively similar. Group 1 was significantly different from all other groups (groups 2-6). Groups 4, 5, and 6 each showed significant differences compared to all other groups, demonstrating clear and consistent treatment effects. These findings confirm that treatment, particularly in group 6, produced optimal and consistent effects in enhancing BDNF levels. Thus, coffee cherry extract has been shown to increase BDNF levels in rats.

This study has several limitations. First, the study only used animal subjects (male Wistar rats), so the results may not directly translate to human patients with diabetes-associated cognitive impairment. Second, the intervention period was relatively short, and long-term neuroprotective effects of coffee cherry extract remain unknown. Third, due to the short duration and limited sample size, several other parameters (e.g., oxidative stress markers such as MDA and SOD, inflammatory cytokines such as TNF-α and IL-6, and other behavioral tests) could not be measured or analyzed. Future studies with longer intervention periods, larger sample sizes, and more comprehensive parameters (including oxidative and inflammatory biomarkers) are needed to confirm and extend these findings.

DISCUSSION

The present study demonstrated that induction of a high-fat diet (HFD) for two weeks followed by intraperitoneal streptozotocin (STZ) injection successfully established a type 2 diabetes mellitus (T2DM) rat model, characterized by significantly increased blood glucose levels, impaired spatial memory performance in the Y-maze test, and reduced brain-derived neurotrophic factor (BDNF) levels compared with controls ($p < 0.05$). These metabolic and cognitive deficits are consistent with previous studies reporting that HFD induces both peripheral and central insulin resistance, while STZ selectively damages pancreatic β-cells leading to chronic hyperglycemia.[17,18]

Extending these findings, a study reported that administration of a high-fat diet (HFD) to female mice expressing human placental lactogen (hPL) during pregnancy causes a decrease in BDNF expression in the hippocampus as well as disrupting maternal behavior and neural stem cell proliferation.[19] Moreover, in line with these observations, liraglutide has been reported to improve cognitive dysfunction and hyperlocomotion in rats through the reduction of TNF-α, while low levels of BDNF contribute to the pathogenesis of diabetes and its complications, including insulin resistance, metabolic dysfunction, and diabetes-related cognitive impairment.[20,21] Further supporting this mechanism, a study reported that chronic hyperglycemia in rats causes a decrease in BDNF levels in the hippocampus through multiple pathological mechanisms and epigenetic inactivation of the REST gene,

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which contributes to cognitive impairment and neurotoxicity.[22]

Turning to our behavioral findings, Y-maze testing revealed that diabetic groups displayed reduced spontaneous alternation percentage (SAP), indicative of hippocampal dysfunction. However, treatment with coffee cherry extract significantly improved SAP scores, approaching or even exceeding normal values, whereas the metformin group showed only moderate improvement. Importantly, these findings align with recent evidence that polyphenols and chlorogenic acid in coffee cherry exert beneficial effects on the brain, consistent with studies reporting that whole coffee cherry extract improves cognitive function in older adults and that coffee pulp phenolics scavenge free radicals while protecting antioxidant enzymes in cellular models.[10,23] Furthermore, these bioactive compounds have been reported to enhance BDNF expression through activation of the CREB signaling pathway while simultaneously suppressing NF-κB-mediated inflammation. Consistent with this mechanism, the observed elevation of BDNF in treated groups further supports the neuroregenerative potential of coffee cherry extract, with the highest BDNF level observed in the high-dose group, indicating a dose-dependent effect.

These results are corroborated by a study reporting that coffee fruit extract is an effective nutritional stimulator for increasing endogenous BDNF levels, thereby potentially supporting brain health and cognitive function, as well as another study demonstrating that polyphenol-rich coffee cherry extract reduces ROS levels and increases serum and exosomal BDNF, improving reaction time and cognitive function in older adults with mild cognitive decline.[15,24] The neuroprotective mechanisms of coffee cherry extract are indeed multifaceted, as studies report that polyphenol-rich coffee and green coffee bean extract exert antioxidant, anti-inflammatory, and neuroprotective effects against neurodegenerative diseases such as Parkinson's and Alzheimer's through modulation of neurotransmitter pathways and gene expression including A2AR, ESR, NOS, GRIN2A, and APOE.[25,26,27] Therefore, although no direct comparison was conducted, coffee cherry extract, as a natural source of these bioactive compounds, may offer a promising complementary neuroprotective strategy with potentially lower toxicity risks. Notably, the high-dose coffee cherry extract group demonstrated superior outcomes to metformin in both SAP scores and BDNF levels, suggesting direct neurotrophic effects beyond glucose lowering.

CONCLUSION

This study demonstrates that a combination of high-fat diet and streptozotocin successfully induces a type 2 diabetes model

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characterized by hyperglycemia, cognitive impairment, and reduced hippocampal BDNF expression. Administration of coffee cherry extract significantly improved spatial memory performance and increased BDNF levels, suggesting its neuroprotective potential through anti-inflammatory and neurotrophic mechanisms. These findings highlight coffee cherry extract as a promising complementary therapeutic candidate for the prevention and management of diabetes-associated cognitive dysfunction.

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