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Evaluation of sirtuin 3 expression and serum concentrations in relation to biochemical variables in Parkinson's disease

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Abstract

Parkinson's Disease (PD), a prevalent neurodegenerative condition, is typified by a buildup of α-synuclein in the significant nigra and a progressive loss of dopaminergic neurons. In the presented study we aimed to investigate the gene expression and serum levels of SIRT 3 with Tyrosine hydroxylase, Glutathione, Malondialdehyde, interleukin 6 and Tumor necrosis factor in patient with Parkinson disease in compare with healthy group. A case-control study was performed on 90 parkinson patients and 90 control individuals. RT-PCR was used to estimate sirtuin 3 gene expression. The ELISA kits were used to measure serum levels of SIRT 3, TH, Alpha synuclein, Tau protein, IL-6, and TNF. Furthermore, glutathione and malondialdehyde concentration in serum was measured using spectrophotometry method. To clarify the relationship between gene expression and serum levels of Sirtuin 3 in with some biochemical biomarkers in patient with Parkinson disease. Our analysis of gene expression showed significant variations between individuals with Parkinson's disease and healthy individuals. Parkinson's patients displayed markedly reduced gene expression. Furthermore, blood levels of SIRT3, TH and glutathione were considerably lower ($p < 0.01$) in the Parkinson's group than in the control group. In contrast, IL-6, TNF, and MDA levels were significantly elevated ($p < 0.01$) in Parkinson's patients compared to healthy controls.

Keywords: Parkinson disease, Sirtuin 3, Gene expression, RT-PCR, Biomarker

1. Introduction

Parkinson's Disease (PD) is an idiopathic neurological disorder that affects both the motor and non-motor systems. It is a degenerative, long-term neurological disease that mainly affects the elderly, however it can also afflict people considerably younger. Aging, family history, and exposure to environmental pollutants like synthetic heroin or pesticides are all associated with idiopathic Parkinson's disease. It is defined by Lewy. In the substantia nigra, body formation and dopaminergic neuron death [1] According to estimates from the World Health Organization (WHO), there will be 2.1 billion older people in the world by the year 2050 [2], Debilitating motor symptoms are the hallmark of Parkinson's disease, a prevalent movement disorder brought on by age-related progressive neurodegeneration.

Little is understood about its early pathophysiological processes and faulty sequences, despite the fact that it is the second most common neurodegenerative disease [3] Cellular respiration byproducts, ROS and RNS, cause oxidative stress, a major factor in neurodegenerative diseases like Parkinson's, Alzheimer's Huntington's, and ALS [4]. The acetylation/deacetylation of mitochondrial

proteins is one way that mitochondrial functions are changed to react to various types of cellular stress and other metabolic issues [5], Together with SIRT1–SIRT7 [6], SIRT3 is one of the seven sirtuins that regulate mitochondrial activity by modifying proteins involved in the control of cell survival in various physiological and pathological conditions [7]. Reversible protein deacetylase SIRT3 regulates the post-transcriptional modification of significant proteins and plays a role in essential mitochondrial processes [8], Recent research indicates that increasing SIRT3 levels supports mitochondrial homeostasis and could be a promising therapeutic target for a variety of diseases, including neurodegenerative diseases [9].

In one way, SIRT3 regulates the respiratory chain of the mitochondria and reduces oxidative stress, which improves the mitochondria's functionality and prevents the substantial's dopaminergic neurons from degeneration [10,43].

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2. Materials and Methods

2.1 Study subject

A total of 180 blood samples 90 patients and 90 controls from both male and female were collected at Ibn Sina Hospital and Research Hospital, from December 20, 2023, to October 20, 2024, and the patients were between the ages of 50 and 82 years.

2.2 Measurement of the SIRT 3 and some biochemical variables concentrations

5 ml of venous blood was withdrawn from patients and controls by venipuncture of which 3 ml was then placed in plain tubes, and was allowed to clot to be centrifuged later at 4000 rpm for 10 min. The obtained serum was stored at -80°C until use. The remaining 2 ml of blood was pipetted into EDTA-containing tubes for RNA extraction and SIRT 3 gene expression estimation by real-time PCR. The ELISA sandwich kit of Wuhan Fine Biotechnology was used to test the serum of the research group for SIRT 3, IL-6 and TNF levels.

2.3 Quantitation of SIRT3 transcripts by real time PCR

For the genetic test, 2.5 mL of blood was collected into PAXgene blood RNA tubes at 1 day postpartum and stored at -80 °C until processing. Total cellular RNA was isolated from the samples with the AddPrep Total RNA Extraction Kit (AddBio, Korea) as per the manufacturer's instructions. The RNA concentration and purity were assessed spectrophotometrically, and the integrity was evaluated using an Agilent 2100 Bioanalyzer (Agilent, Edinburgh, UK). The cDNA was synthesized using AddScript RT Master (Addbio, Korea). Briefly, the reaction mixture was set in a total of 20 µl in a 0.2 ml PCR tube (Promega, Southampton, UK) following the manufacturer's protocols. SIRT3 was taken from earlier studies. The sequences of the primers are summarized in Table 1. b-Actin mRNA was used as an internal control for normalization of the mRNA levels among the samples. Amplifications were performed in duplicate, using a QuantiTect SYBR Green PCR kit (AddBio, Korea), in the iCycler iQ Real-time PCR Detection System (Thermofisher, USA), according to the methods detailed in the manufacturer's instruction manual.

After 10-min denaturing at 95 °C, 40 cycles of amplification were carried out (denaturing at 95 °C for 10 s, annealing at 60 °C for 45 s, and extension at 72 °C for 1 m). Relative expression quantification was carried out using REST 2009 software version 2.0.13.

Table 1. Primer used for RT-PCR of SIRT 3

	Primer	Sequences	[11]
SIRT 3	Forward	5´-CGGCTCTACACGCAGAACATC-3´	
	Reverse	5´-CAGCGGCTCCCCAAAGAACAC-3´	
β-Actin	Forward	5´-TCATCACCATTGGCAATGAG-3´	
	Reverse	5´-CACTGTGTTGGCGTACAGGT-3´	

3. Data Analysis

Data are presented as mean ± SE. Variables were compared between patient and control groups using ANOVA with t-tests ($p < 0.01$) in SPSS (version 18).

4. Results

4.1. Gene Expression of SIRT3

RT-PCR analysis revealed that SIRT 3 mRNA expression was significantly lower in Parkinson's disease patients compared to healthy controls (figure1). Specifically, mean gene expression decreased from 4.7 in healthy individuals to 2.2 in Parkinson's disease patients. SIRT 3 deletion increased oxidative stress and reduced mitochondrial membrane potential in SNc dopaminergic neurons[12]. SIRT3 overexpression in dopaminergic cells mitigates oxidative stress by enhancing mitochondrial function, reducing ROS generation, preserving mitochondrial membrane potential, and promoting cell survival through mitophagy and inflammation suppression[13]. In Parkinson's disease, reduced SIRT3 expression in the substantia nigra pars compacta is linked to increased MnSOD acetylation, impairing its ability to mitigate mitochondrial oxidative stress and contributing to mitochondrial dysfunction and dopaminergic neuron loss [12].

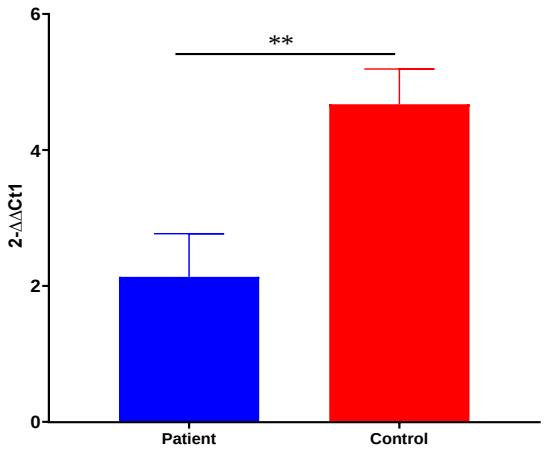

Figure 1. qRT-PCR validation of mRNA expression of SIRT3 in the blood of the patient and control. The statistically significant differences between the groups were calculated using one-way ANOVA. Vertical bars represent Mean+/-SEM, and significant differences between groups are shown with asterisks (**p<0.0001)

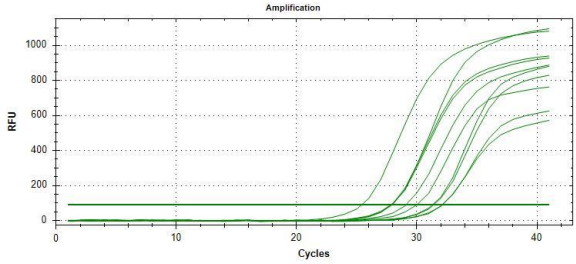

Figure 2. Amplification plot of qRT-PCR for mRNA expression of SIRT3 in the blood of the control group

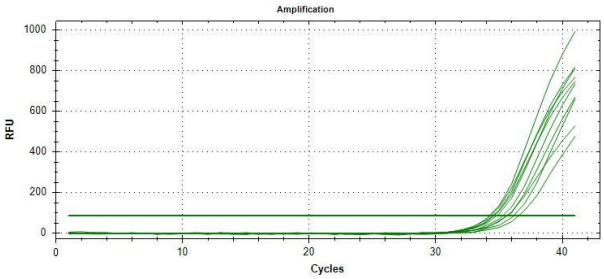

Figure 3. Amplification plot of qRT-PCR for mRNA expression of SIRT3 in the blood of the

4.2. Levels of biochemical variables

Table (2) Levels of biochemical variables measured in the blood plasma of people with Parkinson disease compared to the control group

Biochemical variables	Healthy (n =90)		Patient (n=90)		P value
	Mean	st. error	Mean	st. error	
SIRT 3 (pg/mL)	38.18 ± 1.30		21.06 ± 1.88		< 0.01
TH (pg/mL)	466.87 ± 3.80		300.46 ± 1.50		< 0.01
Alpha synuclein (pg/mL)	25.84 ± 2.07		47.31 ± 1.91		< 0.01
Tau protein (ng/L)	12.85 ± 3.6		41.58 ± 2.97		< 0.01
TNF (pg/mL)	21.17 ± 1.29		28.21 ± 0.84		< 0.01
IL6 (ng/L)	6.79 ± 0.27		9.89 ± 0.72		< 0.01
Glutathione(µmol/L)	2.11 ± 0.10		1.30 ± 0.39		< 0.01
Malondialdehyde(µmol/L)	0.32 ± 0.05		1.14 ±0.07		< 0.01

Table (2) findings demonstrated that the Sirtuin 3 enzyme's activity was significantly lower in Parkinson's disease patients than in the control group, with an average value of (21.06 ± 1.88) compared to (38.18 ± 1.30) in p value less than 0.01 in healthy individuals. These results line up with a variety of studies that indicated low sirtuin 3 level in patients with Parkinson disease [14] [15]. Since the deletion mutation in the Sirtuin 3 enzyme gene is thought to be the primary cause of the decrease in its activity, which raises oxidative stress and damages substantial nigra cells in brain, the cause of the decline in sirtuin 3 enzyme activity is ascribed to both genetic and environmental factors. Sirtuin 3 (SIRT3), a protein deacetylase, stabilizes the electron transport chain (ETC) and lowers oxidative stress, which lessens the effect of subcellular stressors on mitochondria [16]. Age-related inflammation, autophagy, genomic instability, and mitochondrial dysfunction are all significantly reduced by sirtuins, which are downregulated with age [17,44]. people with Parkinson's disease had significantly lower levels of the serum TH enzyme (300.46 ± 19.5) than control group (466.87 ± 37.8). The enzyme activity difference with a p-value of less than or equal to 0.01 between healthy individuals and those with

Parkinson's aligns with numerous studies, in parkinsonism, TH activity is frequently as low as 25% of healthy age-matched controls, and in extreme situations, it can drop as low as 10%. likely due to brain cell damage in the substantia nigra or genetic mutations that reduce dopamine synthesis [18-21]. Parkinson's patients exhibited significantly higher alpha-synuclein levels (47.31 ± 1.91) compared to healthy controls (25.84 ± 2.07) at $p < 0.01$, consistent with prior research. [22]. Actually, the gold standard for evaluating the neuropathology of Parkinson's disease at this time is α-synuclein immunohistochemistry. The findings in Table (3 -1) showed that the amount of tau protein in the PD patients' blood (41.54 ± 2.95) was

significantly higher ($P \leq 0.01$) than in the control group (9.85 ± 3.6), These results demonstrate a substantial rise in Parkinson's patients in comparison to those who are not afflicted, which is in line with the current study [23] [24]. PD objective biomarkers could help with better clinical trial design and interpretation, early and precise diagnosis, and efficient tracking of illness development. The need for a PD biomarker panel is underscored by the complex and heterogeneous nature of Parkinson's disease. The best biomarker candidates are those that represent the underlying degenerative process of Parkinson's disease and may be found in readily available samples, preferably blood [25].

Parkinson's patients have considerably higher levels of the pro-inflammatory markers TNF and IL-6 (28.21 ± 0.84 pg/mL and 9.89 ± 0.72 ng/L, respectively) than healthy controls (21.17 ± 1.29 pg/mL and 6.79 ± 0.27 ng/L), which suggests that the patient group has more systemic inflammation [26] [27] [28] [29] [28]. On the other hand, patients' glutathione levels are much lower (1.30 ± 0.39 µmol/L) than those of healthy people (2.11 ± 0.10 µmol/L), suggesting a weakened antioxidant defense [30], Malondialdehyde, a marker of lipid peroxidation and oxidative stress, is significantly higher in Parkinson's disease patients (1.14 ± 0.07 µmol/L) than in controls (0.32 ± 0.05 µmol/L, $P < 0.01$). This indicates increased oxidative stress and inflammation in patients with Parkinson's disease [31].

Table 3. Comparing several parameters between individuals suffering from parkinson disease and the healthy in various age groups: (50-60 years), (61 - 70 years), and (beyond 71 - 85 years

Biochemical Variables	Patients group 50 – 60 years old	Patients group 61 – 70 y ears old	Patients group 71 – 85 years old
	Mean ± Std. error	Mean ± Std. error	Mean ± Std. error
SIRT 3 (pg/mL)	14.80 ± 3.1 a	12.21 ± 1.68 ab	10.92 ± 0.07 c
TH (pg/mL)	350.42 ± 2.1 a	320.0 ±1.17 a	312.71± 0.9 b
Alpha synuclein (pg/mL)	35.79 ± 1.1 a	41.9299 ± 0.98 b	47.3646 ± 0.87 c
Tau protein (ng/L)	12.61 ± 0.25 a	13.61 ± 3.1 a	14.09 ± 1.28 b
TNF (pg/mL)	26.92 ± 1.25 a	26.45 ± 0.98 a	30.07 ± 1.5 ab
IL6 (ng/L)	10.93 ± 0.024 a	9.98 ± 0.08 a	9.35 ± 1.1 a
Glutathione(µmol/L)	3.05 ± 3.15 a	2.37 ± 0.09 ab	2.00 ± 1.1 c
Malondialdehyde(µmol/L)	1.01 ± 0.036 a	1.32 ± 0.05 ab	1.07 ± 0.09 a

It is believed that aging is a stochastic process that combines predictable and random effects, reducing cellular repair and compensation mechanisms and causing an accumulation of unrepaired cellular damage [32]. In addition to analyzing the impact of age within the patient group by splitting it into three age groups (50 - 60 years), (61 - 70 years), and (71 – 85 years), the effect of age on all biochemical variables in the serum of the patient and control groups was also investigated. SIRT3 levels stay constant from (50–60) to (61–70) before sharply declining in the (71–85) years old group at a probability ($p \leq 0.05$), suggesting reduced mitochondrial activity with age, SIRT3 tends to decrease with age, which can be explained by a number of ways for example decreased availability of NAD+ [33], Oxidative stress accumulation and a decrease in mitochondrial biogenesis [34]. Dopamine and tyrosine hydroxylase (TH) steadily decrease in all groups at a probability ($p \leq 0.05$), potentially indicating declining dopaminergic activity, Aging involves a progressive loss of dopaminergic neurons and receptors, particularly in the substantia nigra. This neuronal decline reduces dopamine synthesis,

resulting in lower levels of dopamine and tyrosine hydroxylase [35] [36]. Elevated alpha-synuclein, tau, and beta-amyloid ($p \leq 0.05$) correlate with increased neurodegeneration risk. Aging-related neuronal damage releases tau; hyperphosphorylation promotes aggregation and hinders clearance due to reduced microtubule affinity. Age-related blood-brain barrier impairment may also contribute to tau leakage into the bloodstream. Accumulating beta-amyloid, tau, and alpha-synuclein, along with elevated TNF and IL-6, further heighten neurodegenerative risk. Aging's oxidative stress disrupts ROS/antioxidant balance, activating inflammatory pathways and cytokine production. [37] [38]. Glutathione, stable in younger individuals, declines significantly in older groups (71 – 85) years old at a probability ($p \leq 0.05$), suggesting impaired antioxidant capacity and it may be related to Due to decreased enzyme activity and restricted precursor availability, particularly cysteine, glutathione synthesis, which is dependent on enzymes like Gamma-Glutamylcysteine Ligase (GCL), decreases with age [39] or/ and Aging increases cellular ROS production, accelerating glutathione consumption and depleting reduced GSH. Malondialdehyde (MDA), an indicator of oxidative stress, increases from ages 61-70.[40].

Table 4. Comparing several parameters between individuals suffering from Parkinson disease and the healthy in age groups (50 – 60) years old.

Biochemical variables	**Control group 50 – 60 years old**	**Patients group 50 – 60 years old**
	Mean ± Std. error	**Mean ± Std. error**
SIRT3 (pg/mL)	35.53 ± 3.11 a	14.80 ± 3.1 c
TH (pg/mL)	464.50 ± 2.8 bc	350.42 ± 2.1 a
Alpha synuclein (pg/mL)	27.46 ± 0.25 a	35.79 b ± 1.1
Tau protein (ng/L)	4.907 ± 0.32	12.61 ± 0.25 c
TNF (pg/mL)	18.44 ± 0.27 a	26.92 ± 1.25 ab
Beta amyloid (pg/mL)	74.25 ± 1.35 a	161.71 ± 1.28 b
IL6 (ng/L)	6.31 ± 0.13 a	10.93 ± 0.024 c
Glutathione(µmol/L)	2.01 ± 2.69 bc	3.05 ± 3.15 c
Malondialdehyde(µmol/L)	0.37 ± 0.089 a	1.01 ± 0.036 b

Different letters presented horizontally signify a statistically significant difference at the probability level ($P \leq 0.05$).

Table 5. Comparing several parameters between individuals suffering from Parkinson disease and the healthy in age groups (61 – 70) years old.

Biochemical variables	**Control group 61 – 70 years old**	**Patients group 61 – 70 years old**
	Mean ± Std. error	**Mean ± Std. error**
SIRT 3 (pg/mL)	32.80 ± 1.28 b	12.21 ± 1.68 c
TH (pg/mL)	433.02 ± 0.95 ab	320.0 ±1.17 b
Alpha synuclein (pg/mL)	26.8694 ± 0.08 a	41.9299 ± 0.98 b
Tau protein (ng/L)	4.91 ± 2.8 a	13.61 ± 3.1 c
TNF (pg/mL)	21.96 ± 0.78 a	26.45 ± 0.98 bc
Beta amyloid (pg/mL)	85.30 ± 1.9 a	177.36 ± 0.9 b
IL6 (ng/L)	7.22 ± 0.05 ab	9.98 ± 0.08 bc
Glutathione(µmol/L)	0.51 ± 0.078 a	2.37 ± 0.09 bc
Malondialdehyde(µmol/L)	0.32 ± 0.08 a	1.32 ± 0.05 b

Different letters presented horizontally signify a statistically significant difference at the probability level ($P \leq 0.05$).

Table 6. Comparing several parameters between individuals suffering from Parkinson disease and the healthy in age groups (71 – 85) years old

Biochemical variable	Control group 71 – 85 years old	Patients group 71 – 85 years old
	Mean ± Std. error	Mean ± Std. error
SIRT 3 (pg/mL)	29.19 ± 0.08c	10.92 ± 0.07 ab
TH (pg/mL)	401.871± 1.2 c	312.71± 0.9 a
Alpha synuclein (pg/mL)	27.15± 0.67a	47.3646 ± 0.87
Tau protein (ng/L)	2.8 ± 8.5 a	14.09 ± 1.28 c
TNF (pg/mL)	22.98 ± 1.9 a	30.07 ± 1.5 c
Beta amyloid (pg/mL)	82.72 ± 0.9 a	165.76 ± 0.85 b
IL6 (ng/L)	6.88 ± 1.5 ab	9.35 ± 1.1 abc
Glutathione(µmol/L)	1.07 ± 0.95 ab	2.00 ± 1.1 bc
Malondialdehyde(µmol/L)	0.26 ±0.04 a	1.07 ± 0.09 b

Different letters presented horizontally signify a statistically significant difference at the probability level (P ≤ 0.05)

4.3 Liner correlation coefficient between Sirtuin 3 and clinical variables

Table 7. Show the Liner correlation coefficient between Sirtuin 3 and clinical variables

	SIRT 3
	Patients group
TH	0.537
Tau	-0.340
Syn	-0.409
TNF	-0.302
IL6	-0.462
Amy	-0.546
MDA	-0.612
GSH	0.441

According to the table (3-9), SIRT3 has a significant association probability of (p ≤ 0.05) with TH (0.537), and GSH (0.441), indicating a relationship between elevated SIRT3 levels and improved neuroprotection and antioxidant capacity [41]. On the other hand, SIRT3 has negative correlations with MDA (-0.612) suggesting a function in reducing metal buildup and oxidative stress [42]. SIRT3 could decrease oxidative stress, metal buildup, inflammation, and neurodegeneration, as evidenced by its substantial negative relationships with MDA, inflammatory markers (TNF, IL6), and neurodegenerative markers (Tau, Syn, Aβ) [41].

These results imply that SIRT3 protects against neurodegeneration, oxidative stress, and inflammation, possibly via increasing antioxidant capacity.

5. Conclusion

Since dopaminergic neurons are susceptible to oxidative stress and mitochondrial malfunction, SIRT3 plays a critical role in Parkinson's disease. It is becoming more and more evident that SIRT3 plays a crucial function in maintaining mitochondrial integrity and brain health in Parkinson's disease. These findings suggest that SIRT3 may protect neurons from oxidative stress, making it a potential therapeutic target.

References

1. Beitz, J.M., Parkinson's disease: a review. Front Biosci (Schol Ed), 2014. 6(1): p. 65-74.
2. Zhao, J., et al., The molecular mechanism of aging and the role in neurodegenerative diseases. Heliyon, 2024. 10(2): p. e24751.
3. Cramb, K.M.L., et al., Impaired dopamine release in Parkinson's disease. Brain, 2023. 146(8): p. 3117-3132.
4. Metodiewa, D. and C. Kośka, Reactive oxygen species and reactive nitrogen species: relevance to cyto(neuro)toxic events and neurologic disorders. An overview. Neurotox Res, 2000. 1(3): p. 197-233.
5. Sakai, T., et al., Design, synthesis and structure–activity relationship studies of novel sirtuin 2 (SIRT2) inhibitors with a benzamide skeleton. Bioorganic & Medicinal Chemistry, 2015. 23(2): p. 328-339.
6. Al-Sadoon, H.N.L.A.-N.a.M.B.H., Evaluation of the Level of Sirtuin7 and Some Biochemical Parameters in Patients with Cardiovascular

Disease. Egyptian Journal of Veterinary Sciences, 2025. 56: p. 1201-1206.
7. Ansari, A., et al., Function of the SIRT3 mitochondrial deacetylase in cellular physiology, cancer, and neurodegenerative disease. Aging Cell, 2017. 16(1): p. 4-16.
8. Schwer, B., et al., The human silent information regulator (Sir)2 homologue hSIRT3 is a mitochondrial nicotinamide adenine dinucleotide-dependent deacetylase. J Cell Biol, 2002. 158(4): p. 647-57.
9. Zhang, S., Y. Ma, and J. Feng, Neuroprotective mechanisms of ε-viniferin in a rotenone-induced cell model of Parkinson's disease: significance of SIRT3-mediated FOXO3 deacetylation. Neural Regen Res, 2020. 15(11): p. 2143-2153.
10. Yapryntseva, M.A., et al., Mitochondrial sirtuin 3 and various cell death modalities. Front Cell Dev Biol, 2022. 10: p. 947357.
11. Sultan, S., N. Alzahrani, and K. Al-Sakkaf, The postpartum effect of maternal diabetes on the circulating levels of sirtuins and superoxide dismutase. FEBS Open Bio, 2018. 8(2): p. 256-263.
12. Shi, H., et al., Sirt3 protects dopaminergic neurons from mitochondrial oxidative stress. Hum Mol Genet, 2017. 26(10): p. 1915-1926.
13. Jiang, D.Q., et al., SIRT3 expression alleviates microglia activation-induced dopaminergic neuron injury through the mitochondrial pathway. Exp Ther Med, 2022. 24(5): p. 662.
14. Trinh, D., et al., Parkinson's disease pathology is directly correlated to SIRT3 in human subjects and animal models: Implications for AAV.SIRT3-myc as a disease-modifying therapy. Neurobiology of Disease, 2023. 187: p. 106287.
15. Al-Mzori, N.A.M., Evaluation of Sirtuin-3 level and some biochemical parameters in people with Parkinson's disease and study the effect of the leucaena plant on male mice induced with Parkinson's disease M.Sc. Thesis in Chemistry / Biochemistry Supervised by Assistant Professor Dr. Mohammed. 2023, University of mosul.
16. Gleave, J.A., et al., Sirtuin 3 rescues neurons through the stabilisation of mitochondrial biogenetics in the virally-expressing mutant α-synuclein rat model of parkinsonism. Neurobiology of Disease, 2017. 106: p. 133-146.
17. Morris, B.J., Chapter 4 - Sirtuins and aging, in Sirtuin Biology in Medicine, K. Maiese, Editor. 2021, Academic Press. p. 49-77.
18. Tabrez, S., et al., A synopsis on the role of tyrosine hydroxylase in Parkinson's disease. CNS Neurol Disord Drug Targets, 2012. 11(4): p. 395-409.
19. Napolitano, A., P. Manini, and M. d'Ischia, Oxidation chemistry of catecholamines and neuronal degeneration: an update. Curr Med Chem, 2011. 18(12): p. 1832-45.
20. Kawahata, I. and K. Fukunaga, Degradation of Tyrosine Hydroxylase by the Ubiquitin-Proteasome System in the Pathogenesis of Parkinson's Disease and Dopa-Responsive Dystonia. International Journal of Molecular Sciences, 2020. 21(11): p. 3779.
21. Manar K. Ahmed1*, M.I.M., Sarab D. Al-Shamaa2, C.o.S. 1Department of Biology, University of Mosul, Mosul, Iraq, and A.-H.U. 2Department of Medical Laboratory Technologies, Mosul, Iraq, Correlation of Tyrosine Hydroxylase, Orexin, and NFL Concentration with Parkinson's Disease. Texila International Journal of Public Health, 2025.
22. Chang, C.W., et al., Plasma and Serum Alpha-Synuclein as a Biomarker of Diagnosis in Patients With Parkinson's Disease. Front Neurol, 2019. 10: p. 1388.
23. Ren, J., et al., Plasma α-synuclein and phosphorylated tau 181 as a diagnostic biomarker panel for de novo Parkinson's disease. 2022. 161(6): p. 506-515.
24. Chojdak-Łukasiewicz, J., et al., Plasma tau protein and Aβ42 level as markers of cognitive impairment in patients with Parkinson's disease. Adv Clin Exp Med, 2020. 29(1): p. 115-121.
25. Youssef, P., et al., Evaluation of plasma levels of NFL, GFAP, UCHL1 and tau as Parkinson's disease biomarkers using multiplexed single molecule counting. Sci Rep, 2023. 13(1): p. 5217.
26. El-Kattan, M.M., et al., Relation of serum level of tumor necrosis factor-alpha to cognitive functions in patients with Parkinson's disease. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 2022. 58(1): p. 25.

27. Padureanu, R., C.V. Albu, and R.R. Mititelu, Oxidative Stress and Inflammation Interdependence in Multiple Sclerosis. 2019. 8(11).
28. Dufek, M., et al., Interleukin-6 May Contribute to Mortality in Parkinson's Disease Patients: A 4-Year Prospective Study. Parkinson's Disease, 2015. 2015(1): p. 898192.
29. Scalzo, P., et al., Serum levels of interleukin-6 are elevated in patients with Parkinson's disease and correlate with physical performance. Neuroscience Letters, 2010. 468(1): p. 56-58.
30. Mischley, L.K., et al., Glutathione as a Biomarker in Parkinson's Disease: Associations with Aging and Disease Severity. Oxid Med Cell Longev, 2016. 2016: p. 9409363.
31. Chang, K.-H. and C.-M. Chen, The Role of Oxidative Stress in Parkinson's Disease. Antioxidants, 2020. 9(7): p. 597.
32. Kirkwood, T.B., The most pressing problem of our age. Bmj, 2003. 326(7402): p. 1297-9.
33. Hirschey, M.D., et al., SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature, 2010. 464(7285): p. 121-5.
34. Ahn, B.H., et al., A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. Proc Natl Acad Sci U S A, 2008. 105(38): p. 14447-52.
35. Berry, A.S. and V.D. Shah, Aging Affects Dopaminergic Neural Mechanisms of Cognitive Flexibility. 2016. 36(50): p. 12559-12569.
36. Karrer, T.M., et al., Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis. Neurobiology of Aging, 2017. 57: p. 36-46.
37. Molinuevo, J.L., et al., Current state of Alzheimer's fluid biomarkers. Acta Neuropathol, 2018. 136(6): p. 821-853.
38. Bjørklund, G., et al., The glutathione system in Parkinson's disease and its progression. Neuroscience & Biobehavioral Reviews, 2021. 120: p. 470-478.
39. Aoyama, K. and T. Nakaki, Glutathione in Cellular Redox Homeostasis: Association with the Excitatory Amino Acid Carrier 1 (EAAC1). Molecules, 2015. 20(5): p. 8742-58.
40. Jomova, K., et al., Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. 2023. 97(10): p. 2499-2574.
41. Zhang, H., et al., Role of Sirtuin 3 in Degenerative Diseases of the Central Nervous System. Biomolecules, 2023. 13(5): p. 735.
42. Ding, Y., et al., Protective role of sirtuin3 against oxidative stress and NLRP3 inflammasome in cholesterol accumulation and foam cell formation of macrophages with ox-LDL-stimulation. Biochem Pharmacol, 2021. 192: p. 114665.
43. Khan, S., Jam, F. A., Shahbaz, M., & Mamun, M. A. (2018). Electricity consumption, economic growth and trade openness in Kazakhstan: evidence from cointegration and causality. OPEC Energy Review, 42(3), 224-243.
44. Kashmeeri, S., Yaacob, M. R. B., Khalique, M., Hina, K., & Jam, F. A. (2021, November). A Conceptual Paper on the Role of Technologies in SMEs Islamabad Pakistan. In International Conference on Business and Technology (pp. 901-906). Cham: Springer International Publishing.