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Repurposing Quercetin In Treating Parkinson's Disease With Network Based Protein-Protein Interactions And Molecular Docking Studies.

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Abstract
Quercetin a flavonoid found in fruits and vegetables is well known for its antioxidant, anti-inflammatory, antimicrobial, and neuroprotective properties. An insilico approach has been adapted in this study for repurposing Quercetin as a potential drug candidate for the treatment of Parkinson's disease (PD) and other neurodegenerative disorders. For this, we used STRING platform to understand protein-protein interactions and perform MCL cluster analysis to bring an intercorrelation among the genes contributing to PD. From the results of the network and PPI analysis, four genes, Alpha-synuclein (SNCA), Microtubule-associated protein tau (MAPT), Leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2), and Parkin (PRKN) were selected for molecular docking to predict interactions between the predicted genes and Quercetin. The results of this study suggest that SNCA, MAPT, LRRK2, and PRKN have a binding affinity with Quercetin rendering its repurposing for the treatment of PD.

Keywords: Quercetin, Parkinson's disease, neurodegenerative disorders, protein-protein interactions, molecular docking, SNCA, PRKN, MAPT, LRRK2.

1. Introduction

In recent times, Quercetin has been used extensively in different therapeutics due to its antioxidant, anti-inflammatory, antimicrobial, and neuroprotective properties [1-3]. Quercetin is 3,3',4',5,7-pentahydroxyflavone belongs to the family of dietary flavonoids. It is found in various vegetables, fruits, grains, etc [4,5]. This polyphenol as a bioactive compound is observed to interact with various enzymes either inhibiting or activating them and exhibits more bioavailability compared to other phytochemicals [5,6]. Therefore, it is important to explore possible potential pharmaceutical applications of Quercetin. Further, it was observed that Quercetin can inhibit the formation of Alpha-Synuclein aggregates [7,8], a characteristic feature of PD rendering Quercetin a potential drug candidate to slow down the progression of the disease. It is estimated that by 2050, there will be around 12 million people globally suffering from this disease [9]. So, there is a dire need to develop novel treatments and preventive interventions to tackle this disease. As the prognosis of the disease

varies, it is important to customize treatments for geographical locations as well. Several theories were proposed on the pathobiology of PD, a progressive neurodegenerative disorder but still, there is much to be explored in the progression and treatment of the disease [10-12]. The research studies carried out on mutation accumulation suggest that PRKN, SNCA, MAPT, and LRRK2 genes play a significant role in the progression of the disease and there is a need to carry out studies on these for developing effective treatment strategies for PD[13]. STRING [14] is a database with known and predicted protein-protein interactions from experimental as well as computational prediction methods.

In this study, we use STRING to understand protein-protein interactions and perform MCL cluster analysis to bring an intercorrelation among the genes contributing to PD [15]. Finally, using dockthor, docking studies were carried out with these predicted genes with Quercetin [16]. Insilico studies help in repurposing compounds like Quercetin with established pharmacological properties, and associated interactions with targets linked with PD paving the way to novel drugs and treatment methods. Our study provides insights into repurposing Quercetin for the treatment of PD and its role in slowing down the progression of the disease.

1. Methods

The chemical structure of Quercetin was obtained from the PubChem database [17].

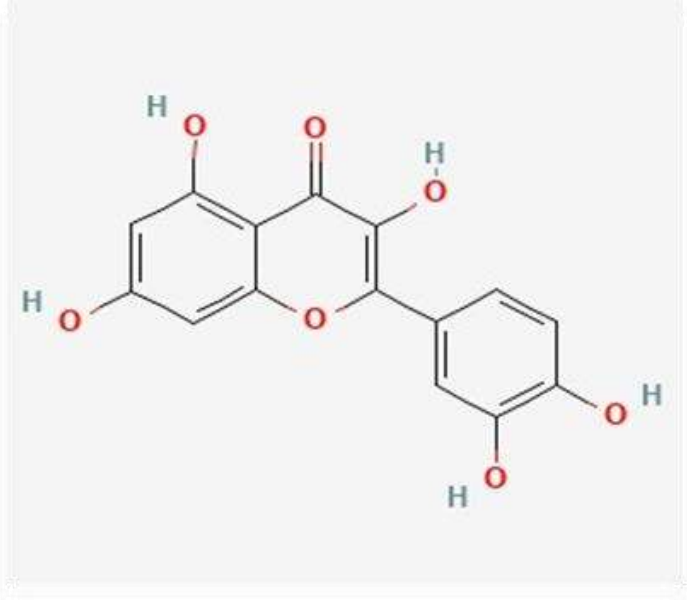

Fig: 1 Structure of Quercetin

As seen in Figure 1, in Quercetin, the OH groups are present at 3, 3′, 5, 7 positions and is an aglycone. Corresponding Quercetin glycoside with increased water solubility may be created by substituting one of the OH groups with the glycosyl group. Chemical structures were obtained from PubChem.

2.1 Quercetin Target Gene Identification

String database is a platform that integrates various databases, experimental and computational data for predicting protein-protein interactions. STRING uses different prediction techniques, such as co-expression analysis, text mining, and evolutionary conservation, to deduce functional relationships between proteins. For this purpose, Parkinson's disease for Homosapien is chosen. From the resultant network, performing MCL cluster analysis, *Alpha-synuclein* (SNCA), Microtubule-

associated protein tau (MAPT), Leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2), and *Parkin* (PRKN) were chosen.

2.2 Molecular Docking studies

To carry out molecular docking studies, PDB files of SNCA, MAPT, LRRK2, and PRKN are taken from Protein Data Bank (PDB) and are 3Q27, 2MZ7, 6DLO, and 6GLC respectively (https://www.rcsb.org). MMFF94S force field is used as a scoring function in the Dockthor program[16], which was developed by the GMMSB/LNCC group. Dockthor predicts the binding mechanism and affinity to target protein or receptor and helps in identifying potential drug candidates. A suitable grid center was chosen and assigned for docking.

3. Results

In the STRING platform, a search for PD and its associated protein -protein interactions (PPI) were initiated. The resulting data indicates 44 nodes, 515 edges, with an average node degree of 23.4avg and local clustering coefficient of 0.781 as shown in Fig.2.

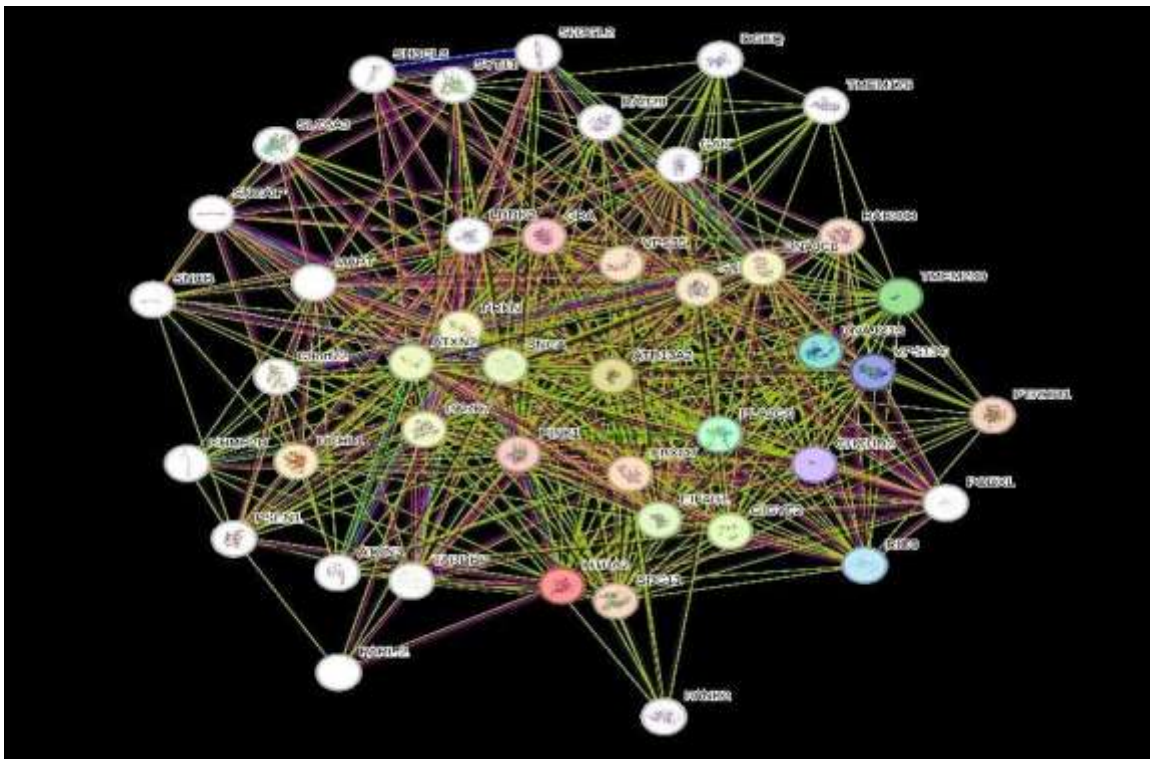

Fig: 2 Protein-protein interactions associated with PD

We consider the strength factor with a threshold value of 2 for PPI maximum false discovery rate and the interactions that meet the threshold are considered which are fewer PPI compared to Fig.2 as shown in Fig.3. below. MCL (Markov Cluster Algorithm) analysis is performed on these PPI to identify clusters with high mapping and is as shown in Figure 4 [15].

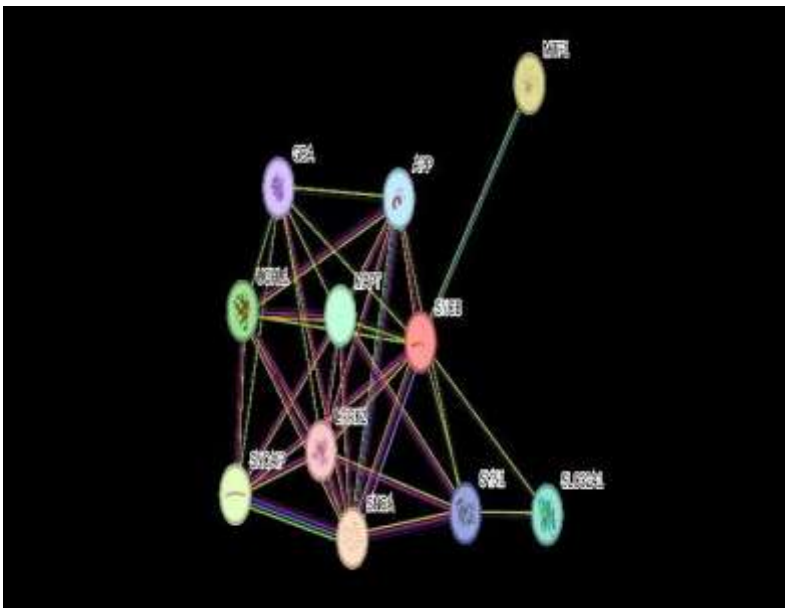

Fig: 3.PPI interactions with strength greater than equal to 2

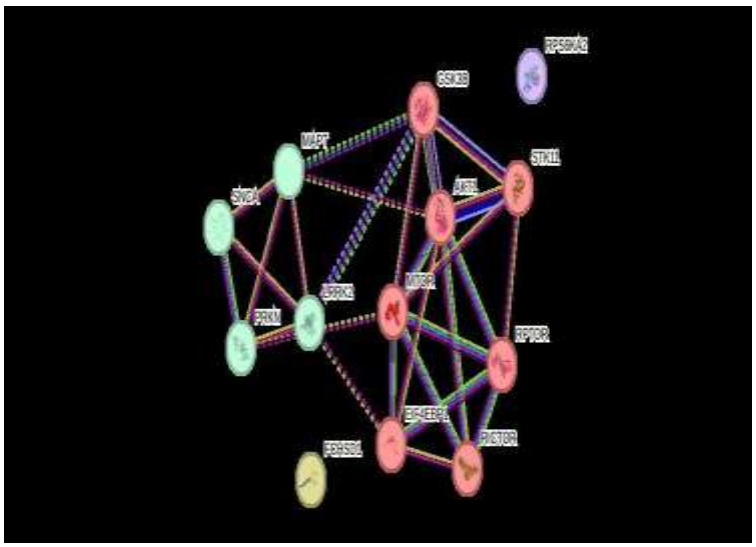

Fig: 4. PPI after MCL cluster analysis

MCL is based on the simulation of stochastic flow and identifies clusters as regions with high flow. From Fig. 4, it is evident that the cluster consisting of hub genes in the network SNCA, MAPT, LRRK2, and PRKN are marked green and play a critical role in the progression of PD.

In PD, Lewy bodies and Lewy neurites accumulate α-synuclein, a highly soluble unfolded protein. It is associated with mutations in the SNCA gene. Protein mapped to neurodegenerative disorders (MAPT) may not be directly linked with PD like SNCA but exhibits strong relevance in neurodegeneration and cognitive impairment.

LRRK2 gene mutations are frequent hereditary causes of PD and have attracted the attention of many researchers to understand the various factors associated with it [18-20]. PD is linked to mutations of the gene PARK2 which codes for the protein PRKN. It is an essential component in UPS (ubiquitin-proteasome system) which plays a significant role in regulating protein quality and homeostasis. Malfunctioning of UPS can lead to increased protein accumulations aggravating neurodegeneration [21]. From the results of the network and PPI analysis, four genes, SNCA, MAPT, LRRK2, and PRKN were selected for docking with Quercetin to understand their binding affinity. From docking studies given in Table 1 and previous experimental data, it is observed that SNCA has possible binding sites

to interact with Quercetin. Further, studies also reveal that hydroxyl groups present in Quercetin prevent aggregation of alpha-synuclein obstructing nucleation and elongation phases [22]. Quercetin interacts with MAPT through several binding sites and regulates the activities of kinases and phosphatases, a key factor in tauopathies [23]. Experimental data and computational analyses indicate that Quercetin modifies the signaling pathways improving neurogenesis. By binding with Quercetin, dysfunction of LRRK2 is modulated protecting neurons [24]. Mitochondrial dysfunction is associated with PRKN-mediated mitophagy failure resulting from oxidative stress which can be regulated by Quercetin through its scavenging action on reactive oxygen species [25].

Table: 1 Binding affinity and docking parameters for the hub genes with Quercetin

S.No.	Gene	PDB Name	*Affinity* kcal/mol	*Total Energy* kcal/mol	*vdW Energy* kcal/mol	*Elec. Energy* kcal/mol
1	SNCA	3Q27	-7.821	4.406	-15.329	-34.165
2	MAPT	2MZ7	-10.098	975.441	952.739	-43.006
3	LRRK2	6DLO	-7.38	15.338	-7.133	-25.906
4	PRKN	6GLC	-7.576	14.039	-15.118	-19.241

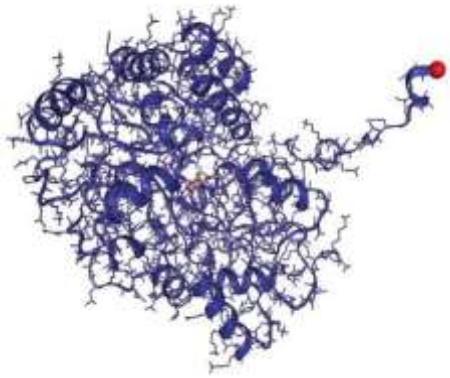

Fig.5 Molecular docking of SNCA with Quercetin

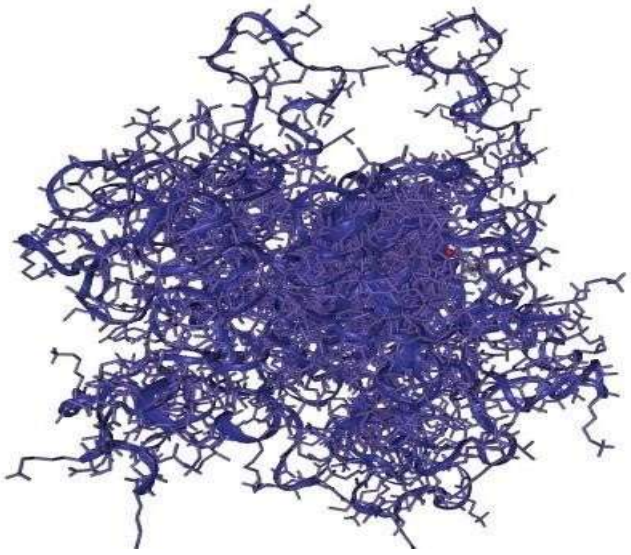

Fig.6 Molecular docking of MAPT with Quercetin

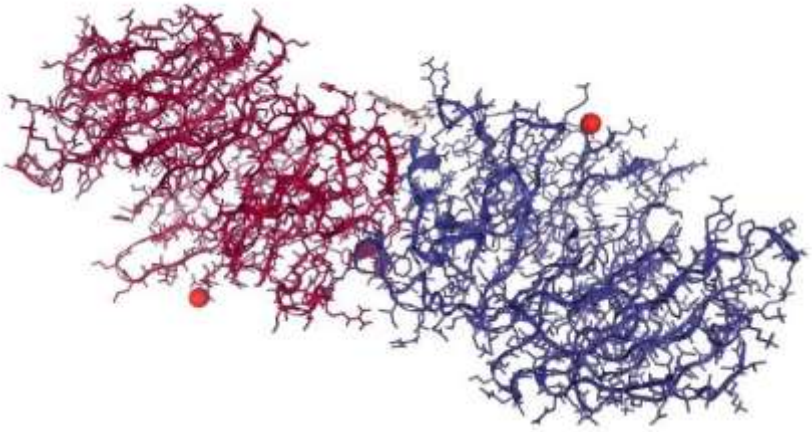

Fig.7 Molecular docking of LRRK2 with Quercetin

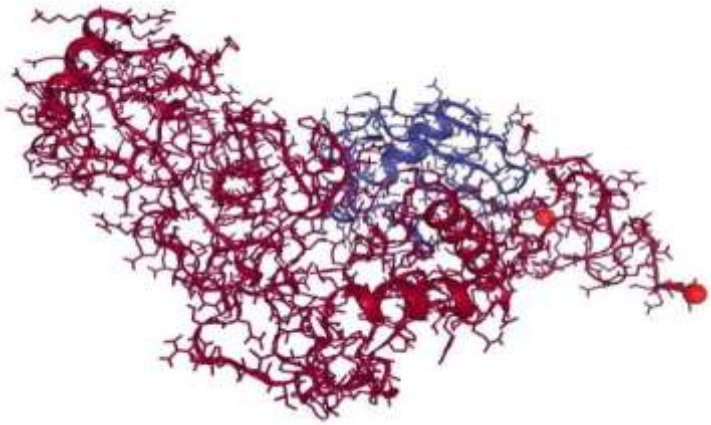

Fig.8 Molecular docking of PRKN with Quercetin

4. Discussion

Flavonoid Quercetin and its derivatives present in fruits and vegetables have the potential to act as bioactives and exhibit therapeutic potential towards neurodegenerative disorders like PD. It is also observed that it enhances cholinergic activity and prevents early onset of these disorders. Quercetin disintegrates the aggregated alpha-synuclein fibrils helping in the removal of already-existing protein aggregates and stops new ones from forming thus stabilizing it in its soluble state thereby stopping pathogenic metamorphosis [8]. Even though various studies establish the efficacy of Quercetin, further research is required to determine the exact mechanism or pathways through which it alleviates PD. Quercetin binding with MAPT is critical and pathological alterations needs to be further investigated and it will have serious implications not only in PD but also other neurological disorders. Antioxidant and anti-inflammatory properties of Quercetin is due to its ability to cross blood-brain barrier (BBB) and promotes mitochondrial biogenesis [26].

5. Conclusions

PD is a complex neurodegenerative disorder involving cognitive and motor impairments. SNCA, MAPT, LRRK2, and PRKN gene mutations are implicated in PD. However, due to the multifactorial nature of the disease with contributing factors like genetic, environmental, aging, etc, it becomes difficult to establish the etiology of the disease. To mitigate this, it is crucial to detect early and adapt a lifestyle that delays the progression of the disease. To treat long-term ailments and lifestyle disorders, it is crucial to use bioactives as they have fewer side effects. For this, Quercetin that is

known for its therapeutic potential is explored. Our findings conclude that SNCA, MAPT, LRRK2, and PRKN have a binding affinity with Quercetin rendering its repurposing as a potential drug candidate for the treatment of PD and other neurodegenerative disorders.

References:

1. M.Azeem, M.Hanif, K.Mahmood, N.Ameer, F. R. S.Chughtai, U..Abid, *Polymer Bulletin (Berlin, Germany)* 1, (2022), https://doi.org/10.1007/s00289-022-04091-8.
2. F. Aghababaei and M. Hadidi. *Pharmaceuticals* **16**, 1020 (2023), doi:10.3390/ph16071020.
3. B.Salehi, L. Machin, L. Monzote, J. Sharifi-Rad, S. M. Ezzat, Md A. Salem, R. M. Merghany, *ACS Omega* **20**, 11849 (2020), doi:10.1021/acsomega.0c01818.
4. P. Subramani, A.D. AlexanderVictor and A. Radhakrishnan. *Pharmacognosy Reviews* **20**, 84 (2016), doi:10.4103/0973-7847.194044.
5. P Prashant, A.Chetna Goswami, S.Rafeeya, K Vinay Pandey, T.Anjali, R.Sarvesh, and G.Darshan, *Future Foods* **9,** 100313 (2024),. doi:10.1016/j.fufo.2024.100313.
6. Dabeek, M.Wijdan , and V.Melissa Marra, *Nutrients* **10,** 2288 (2019), doi:10.3390/nu11102288.
7. Das, S. Sabya, K.Niraj Jha, K. Saurabh . Jha, R. PriyaVerma, M.Ghulam Ashraf, and K Sandeep Singh, *Current Neuropharmacology.,* **21**, 1464 (2023), doi:10.2174/1570159x21666221221092250.
8. E. Srinivasan, G. Chandrasekhar, P. Chandrasekar, K. Anbarasu, A. S. Vickram, Rohini Karunakaran, R. Rajasekaran and P. S. Srikumar, *Frontiers in Medicine*, **18,** 354 **(**2021) https://doi.org/10.3389/fmed.2021.736978
9. Dorsey, E. Ray, *The Lancet Neurology*, **11,** 939 (2018), https://doi.org/10.1016/ s1474-4422(18)30295-3.
10. Emamzadeh, N.Fatemeh, and S.Andrei, *Frontiers in Neuroscience* **12**, 734 (2018). doi:10.3389/fnins.2018.00612.
11. Müller-Nedebock, C. Amica, C. Marieke Dekker, J.Matthew, Farrer, Nobutaka Hattori, Shen-Yang Lim, George, D. Mellick, Irena Rektorová, *npj Parkinson's Disease* **9,** 459 (2023). doi:10.1038/s41531-023-00535-8.
12. G.Foffani, and A.José Obeso, *Neuron* **99**, 1116 (2018) https://doi.org/10.1016/j.neuron.2018.07.028.
13. C.Bandres, Sara, F.Monica Diez, J.Jonggeol, J. Kim, and B.Andrew Singleton. *Neurobiology of Disease* **137,** 104782 (2020), doi:10.1016/j.nbd.2020.104782.
14. Szklarczyk, Damian, K.Rebecca, K.Mikaela, N.Katerina, M.Farrokh, H.Radja, L.Annika Gable, *Nucleic Acids Research* **51**, D638 (2022), doi:10.1093/nar/gkac1000.
15. A. Azad, A Georgios Pavlopoulos, A. Christos, Ouzounis, C.Nikos Kyrpides, and A. Buluç. *Nucleic Acids Research* **46**, e33 (2018), doi:10.1093/nar/gkx1313.
16. Guedes, A.Isabella, S.Leon, B.Costa, B.Karina, Dos Santos, L .Ana Karl, K.Gregório Rocha, M.Iury Teixeira, M.Marcelo Galheigo, *Scientific Reports* **11**, (2021). doi:10.1038/s41598-021-84700-0.
17. S.Kim, J.Chen, T.Cheng, A.Gindulyte, J.He, S.He, Q.Li, B.A.Shoemaker, P.A.Thiessen, B.Yu, L.Zaslavsky, J.Zhang, J., and E. E. Bolton, *Nucleic Acids Res*, **51**, (2023), https://doi.org/.%20https://doi.org/10.1093/nar/gkac956
18. H Tan Sean, K. Venkatanaidu, W.Nicole, H. Tay, Kuan, Y.Chang, Hui Y. Ah, Phui Q. Ng, Hui S. Ho, Hsiao W. Keh, and M.Candasamy. *Biomedicine & Pharmacotherapy* **111,** 765 (2019), doi:10.1016/j.biopha.2018.12.101.

19. Day, J.Oliver, and S.Mullin. *Genes*, **12**, 1006 (2021), https://doi.org/10.3390/genes12071006
20. P.Maiti, ,M. Jayeeta and L.Gary Dunbar. *Translational Neurodegeneration* **6**, (2017). doi:10.1186/s40035-017-0099-z.
21. A.Kurt Jellinger, *J. Cell. Mol. Med.*, **14**, 457 (2010), doi: 10.1111/j.1582-4934.2010.01010.x
22. D.Peña, Samuel, J.García-Pardo, and S.Ventura. *Pharmaceutics* **15**, 839 (2023), doi:10.3390/pharmaceutics15030839.
23. W.Biedrawa, A.Dagmara, *Life*, **12**, 591 (2022), https://doi.org/10.3390/life12040591.
24. Min Zhu, Shubo Han, Anthony L. Fink. *Biochimica et Biophysica Acta (BBA) - General Subjects*, **1830,** 2872 (2013), https://doi.org/doi.org/10.1016/j.bbagen.2012.12.027.
25. Khan, Haroon , *Biomolecules*, **10**, 59 (2019), https://doi.org/10.3390/biom10010059
26. Zhang, Leilei, *Frontiers in Pharmacology*, **13**, (2022), https://doi.org/10.3389/fphar.2022.854249.