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Original research

Caffeine Molecular Target Identification and Protein Interaction Analysis in Alzheimer's Disease

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Abstract:
Caffeine is known to have various biological effects, including its potential to modulate the central nervous system. This study aims to identify the molecular targets of caffeine and explore their relationship with Alzheimer's disease using a bioinformatics approach. The methods used include target prediction using SwissTargetPrediction and SuperPred, target relationship analysis with disease through the DAVID database, protein interaction exploration and enrichment analysis using STRING-DB, and network analysis using Cytoscape. The results showed that from the total targets obtained, there were 20 overlapping targets related to Alzheimer's. Protein interaction analysis revealed 17 nodes with 32 significant interactions, which provide insight into the molecular pathways that caffeine can manipulate in the context of neuroprotection. These findings are in line with various studies showing that caffeine consumption is associated with a reduced risk of Alzheimer's through modulation of the nervous system and inflammation.
Keywords: *Alzheimer, caffeine, enrichment analysis, network pharmacology*

Introduction

Coffee is one of the most popular drinks worldwide, and various groups consume it because of its distinctive taste and stimulant effects (Farah, 2012). In addition to being a popular drink, coffee also has multiple health benefits, mainly because of its bioactive content, one of which is caffeine (Cornelis, 2019). Caffeine is a xanthine alkaloid that is widely found in natural products such as coffee, tea, and cocoa (Eskelinen & Kivipelto, 2010; Gibbs et al., 2015; Mao et al., 2023; Yamaoka-Yano et al., 1999).

Caffeine has effects on health, including cardiovascular (Mendoza et al., 2023; Turnbull et al., 2017), respiratory (Lamba et al., 2021; Seppä-Moilanen et al., 2021; Zhao et al., 2024), smooth muscle effects (Tazzeo et al., 2012), physical and cognitive performance (McLellan et al., 2016; Research & Marriott, 1994). Caffeine affects the central nervous system, increasing alertness and reducing fatigue by inhibiting adenosine receptors that play a role in regulating nerve activity (Chen et al., 2001; Davis et al., 2003; Persad, 2011; Reddy et al., 2024; Research & Marriott, 1994).

Previous studies have shown that moderate coffee consumption may be associated with a variety of health benefits, including a reduced risk of several neurodegenerative diseases such as Parkinson's, Dementia, and Alzheimer's (Barranco Quintana et al., 2007; Chen et al., 2001; Eskelinen & Kivipelto, 2010). Several studies have also indicated that caffeine consumption may improve cognitive function and slow the progression of Alzheimer's disease through suppression of amyloid β activity (Arendash & Cao, 2010). The specific molecular mechanisms underlying caffeine's effects on health must be analyzed to understand its biological activity.

Network pharmacology is one technique used to analyze a compound's molecular target in drug discovery efforts. Integrating biological functions with drug networks is used to find potential targets based on network analysis (Li et al., 2020). Therefore, this study was conducted for molecular network analysis by using bioinformatics approaches to analyze protein interactions related to caffeine compounds and their association with relevant diseases.

Material and Methods

Screening targets and diseases of the compound

SwissTargetPrediction (http://www.swisstargetprediction.ch/) (Daina et al., 2019) and SuperPred (https://prediction.charite.de/) (Nickel et al., 2014) were used to predict caffeine targets. The obtained targets were then merged and duplicates were removed. These targets were then analyzed using the DAVID database (https://davidbioinformatics.nih.gov/) with references

from DISGENET, OMIM, and DISEASE to find their association with various diseases (Huang et al., 2009; Sherman et al., 2022).

To further understand the relationship between these targets and diseases, we used the OMIM database to obtain a list of specific protein targets (Hamosh et al., 2004). The targets from OMIM were then compared with those from SwissTargetPrediction and SuperPred using Venn diagrams to identify overlapping targets (https://bioinfogp.cnb.csic.es/tools/venny/) (Oliveros, 2024).

Protein-Protein Interaction and Enrichment Analysis

These overlapping targets were further analyzed using STRING-DB (https://string-db.org/) to explore protein-protein interactions (PPI). The parameters used include full STRING network for network type, medium confidence (0.400) for required score, medium (5%) for FDR stringency, and *Homo sapiens* for the organism (Szklarczyk et al., 2023).

Furthermore, network analysis was performed using Cytoscape to identify the central role of the targets in the molecular network (Shannon et al., 2003). In addition, enrichment analysis based on Gene Ontology (Gene Ontology Consortium, 2017) and KEGG Pathway (Kanehisa et al., 2022) was performed to identify the biological activities of potential targets using the DAVID database.

Results and Discussion

The identification of caffeine molecular targets using SwissTargetPrediction and SuperPred revealed 114 and 103 targets, respectively. After removing duplications, 208 unique targets were obtained. Disease analysis results from the DAVID database showed that a number of the targets obtained were closely related to Alzheimer's, strengthening the hypothesis that caffeine has neuroprotective potential against this disease (Eskelinen & Kivipelto, 2010; Londzin et al., 2021; Zhou & Zhang, 2021) .

The targeted search against Alzheimer's disease was continued using the OMIM database, which showed 186 targets. These targets were further analyzed using STRING-DB to explore protein interactions. The protein-protein interaction results showed an interaction between 363 targets with 3202 interactions (Figure 2a).

Overlaps between targets obtained from SwissTargetPrediction, SuperPred, and OMIM were analyzed with a Venn diagram to get potential targets, showing 20 overlapping targets (Figure 1, Supplementary File 1). Further analysis of the PPI network obtained from the STRING-DB database was performed with Cytoscape and filtered to create subnetworks between the overlapping targets, which resulted in interactions between 17 targets with 32 interactions (Figure 2b). Network analysis with Cytoscape in betweenness centrality, degree, and closeness centrality values of 17 potential targets can be seen in Supplementary File 2.

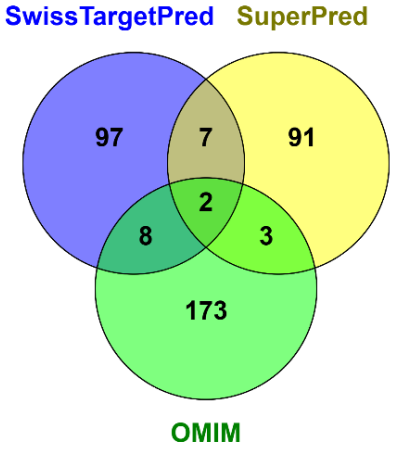

Figure 1. The Venn diagram shows the number of targets and targets overlaps from SwissTargetPrediction, SuperPred, and OMIM databases

Gene Ontology and KEGG Pathway analysis was conducted to determine the function and biological pathway of the target (Figures 3 and 4). Gene Ontology analysis includes biological processes, cellular components, and molecular functions. The biological process analysis showed that the target is related to neurons, such as neuron apoptotic process, proteolysis, positive regulation of neuron apoptotic process, and learning or memory. Alzheimer's disease is characterized by memory deficits and massive neuronal death through apoptotic processes (Calissano et al., 2009; Goel et al., 2022; Roth, 2001; Yang et al., 2008).

Cellular components, one of which is the gamma-secretase complex, are known to be associated with Alzheimer's disease. The gamma-secretase complex is a target of Alzheimer's treatment because of its role in mediating the final cleavage to form amyloid β-peptide. Aβ accumulates in the brain of

Alzheimer's patients, causing neurodegeneration (Hur, 2022; Luo & Li, 2022; Wolfe, 2012).

Molecular functions associated with the target include cysteine-type endopeptidase activity, peptidase activity, aspartic endopeptidase activity intramembrane cleaving, oxidoreductase activity, and cyclin-dependent protein serine/threonine kinase activity. Peptidase and aspartic endopeptidase activity can be associated with gamma-secretase complex activity in producing Aβ-peptide (*QuickGO*, 2025).

The interesting KEGG pathway of the target is associated with Alzheimer's disease, notch signaling pathway, and apoptosis. As is known, apoptosis is associated with the emergence of Alzheimer's disease. In addition, Kapoor & Nation (2020) reported the Notch signaling pathway plays a role in the pathophysiology of the neurodegenerative disease Alzheimer's.

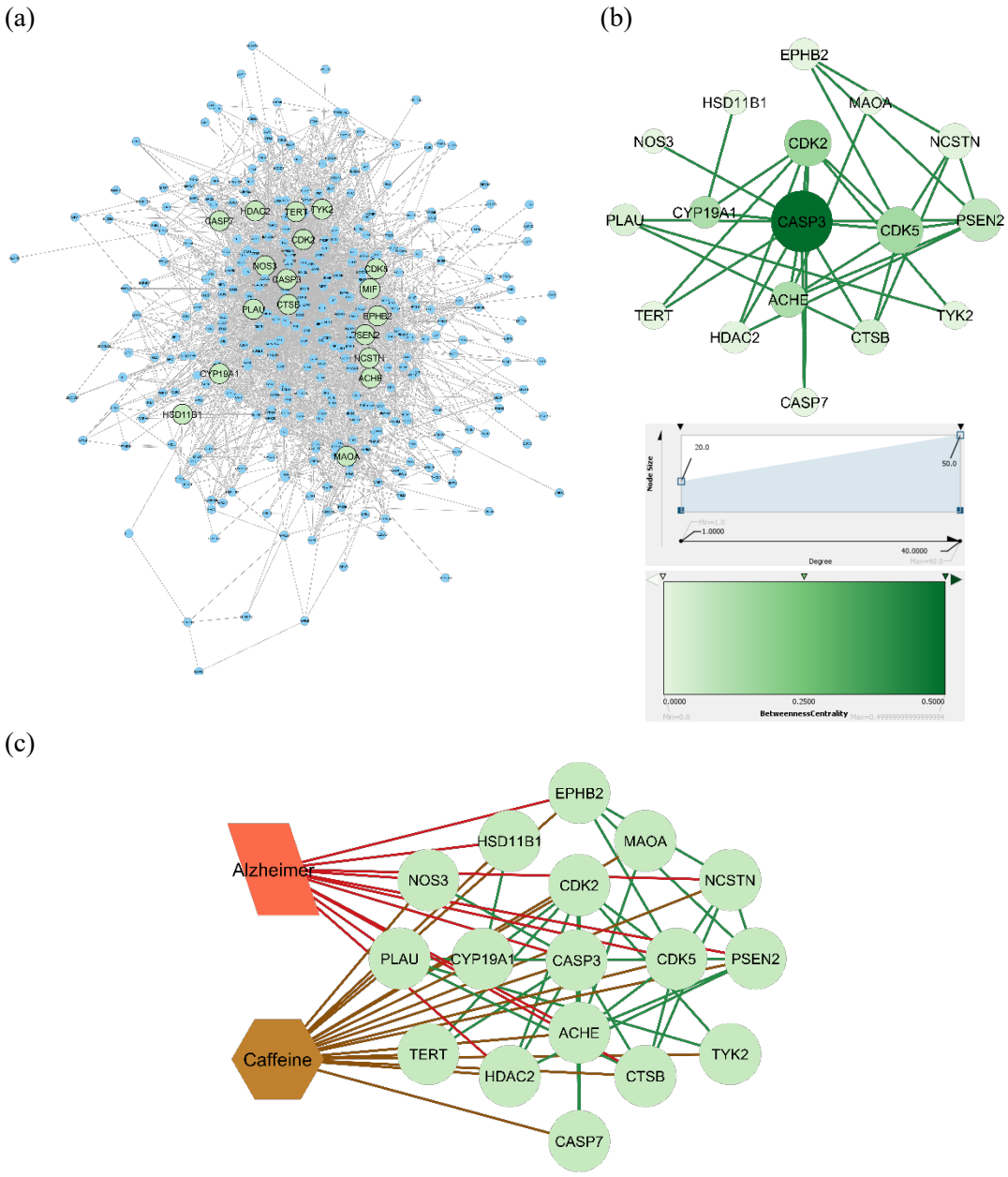

Figure 2. Network topology of targets related to caffeine and Alzheimer's disease. (a) A main network containing targets from SwissTargetPrediction, SuperPred, and OMIM, (b) a Subnetwork based on target overlap, and (c) a Network between potential targets, Alzheimer's disease, and caffeine.

Figure 2c helps us understand the relationship between potential targets associated with caffeine compounds and Alzheimer's disease. All predicted targets are associated with caffeine compounds, and some targets are associated with Alzheimer's disease.

Caffeine can improve cognitive function and reduce beta-amyloid accumulation. Research on the potential of caffeine for the treatment of Alzheimer's disease has been conducted on young adults and aged AD transgenic mice. After caffeine exposure, there was a decrease in Aβ levels in plasma and brain and improved cognitive function (Cao et al., 2009).

Research on the benefits of caffeine coffee in reducing Aβ levels in humans has also been conducted by Kim et al., (2019). The study shows that non-demented older adults who consume coffee ≥2 cups/day have lower Aβ levels than those who consume coffee <2 cups/day so it can be categorized as contributing to reducing the risk of Alzheimer's disease. Increased coffee consumption can potentially reduce cognitive decline by reducing brain Aβ levels that cause oxidative stress and impact neurotoxicity (Gardener et al., 2021).

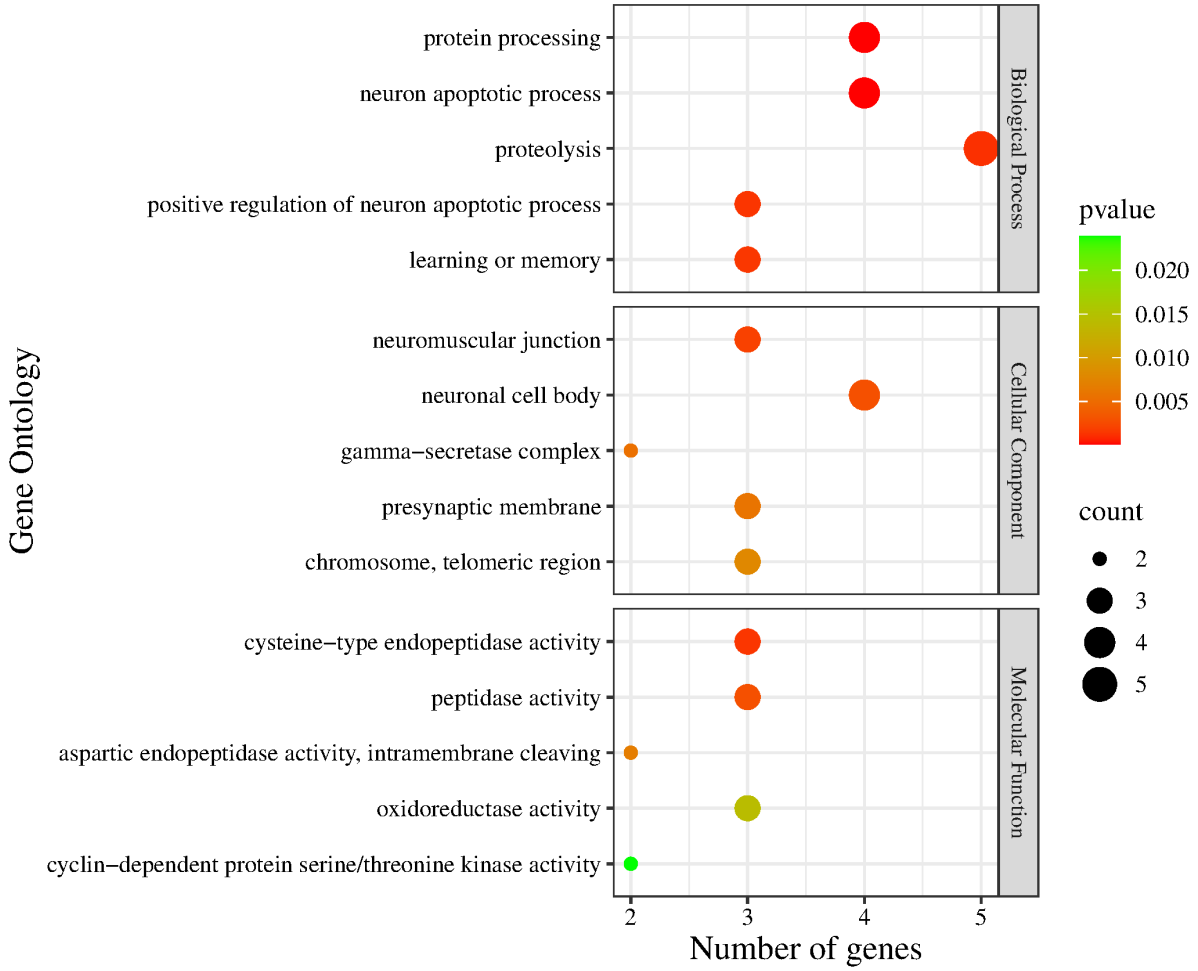

Figure 3. Top 5 gene ontology terms of potential targets with the lowest p-value

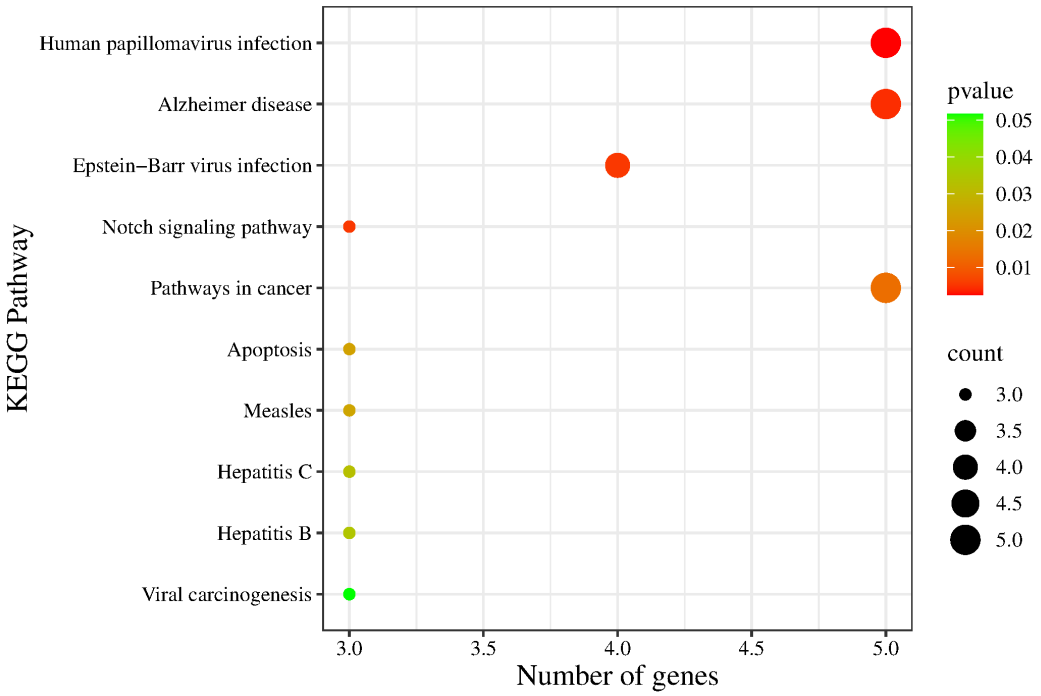

Figure 4. Top 10 KEGG pathway terms of potential targets with the lowest p-value

Based on the identification of potential targets, network analysis shows the relationship between caffeine and PSEN2 targets. PSEN2 is a presenilin group protein that, when mutated, can cause familial Alzheimer's disease (Fedeli et al., 2019; Hur, 2022). Presenilin is known for its role in the Gamma-secretase complex for forming Aβ peptides. Presenilin mutations can increase the Aβ42/Aβ40 ratio, causing Aβ accumulation in the brain and triggering neurodegeneration (Bentahir et al., 2006; De Strooper, 2007).

CASP3 (caspase-3) regulates apoptosis and is reported to be detected in Alzheimer's patients (Khezri et al., 2023; Louneva et al., 2008; Su et al., 2001). Caffeine is reported to suppress caspase-3 activity and protect neurons from Aβ-induced cell death (Chu et al., 2012). Increased caspase-3 activity in neurons with Alzheimer's is believed to be a hallmark of increased apoptosis of these cells so that caspase-3 can be used as a drug target.

Another potential target of caffeine for Alzheimer's therapy is CDK5. CDK5 (Cyclin-Dependent Kinase 5) plays a role in regulating neuronal function. Increased CDK5 activity is found in neurogenerative diseases such as Alzheimer's due to abnormal hyperphosphorylation of CDK5 substrates such as amyloid precursor protein (APP), tau, and neurofilaments. Inhibition of CDK5 activity can reduce neural cell loss by suppressing Aβ induction (Liu et al., 2016). Research on CDK5 expression in the brain of long-tailed macaques related to Alzheimer's disease showed a significant decrease in CDK5 gene expression in the hippocampal region of old monkeys (Rosmanah et al., 2024). CDK5 is found in postmitotic neurons and is helpful for brain development, synaptic plasticity, neuron migration, and memory formation (Allnutt et al., 2020; Dixit et al., 2017; Liu et al., 2016; Shah & Lahiri, 2014).

This research provides an understanding of Alzheimer's therapy through various targets and pathways by exploring the potential of caffeine using a network pharmacology approach. Based on the computational approach, caffeine is promising for neurodegenerative treatment due to its neuroprotective effect. Furthermore, in-silico studies such as molecular docking and molecular dynamics, in-vitro, and in-vivo studies were conducted to validate the mechanism of caffeine in Alzheimer's therapy based on inhibiting molecular targets CASP3, CDK5, and PSEN2.

Conclusion

This study identified that caffeine has molecular targets related to Alzheimer's, namely CASP3, CDK5, and PSEN2. Protein interaction analysis indicated potential regulatory pathways that can be modulated by caffeine in the context of neuroprotection. Inhibition of the expression of

molecular targets CASP3, CDK5, and PSEN2 with caffeine is predicted to suppress Alzheimer's conditions. These findings provide a basis for further research in the development of caffeine-based therapies for neurodegenerative diseases. These results support literature studies stating that caffeine consumption may help reduce the risk of Alzheimer's through complex molecular mechanisms. Further studies are needed to validate caffeine as a promising candidate for treating Alzheimer's.

References

Allnutt, A. B., Waters, A. K., Kesari, S., & Yenugonda, V. M. (2020). Physiological and Pathological Roles of Cdk5: Potential Directions for Therapeutic Targeting in Neurodegenerative Disease. *ACS Chemical Neuroscience*, *11*(9), 1218–1230. https://doi.org/10.1021/ACSCHEMNEURO.0C00096/SUPPL_FILE/CN0C00096_LIVESLIDES.MP4

Arendash, G. W., & Cao, C. (2010). Caffeine and Coffee as Therapeutics Against Alzheimer's Disease. *Journal of Alzheimer's Disease*, *20*, 117–126. https://doi.org/10.3233/JAD-2010-091249

Barranco Quintana, J. L., Allam, M. F., Del Castillo, A. S., & Navajas, R. F. C. (2007). Alzheimer's disease and coffee: a quantitative review. *Neurological Research*, *29*(1), 91–95. https://doi.org/10.1179/174313206X152546

Bentahir, M., Nyabi, O., Verhamme, J., Tolia, A., Horré, K., Wiltfang, J., Esselmann, H., & De Strooper, B. (2006). Presenilin clinical mutations can affect γ-secretase activity by different mechanisms. *Journal of Neurochemistry*, *96*(3), 732–742. https://doi.org/10.1111/J.1471-4159.2005.03578.X

Calissano, P., Matrone, C., & Amadoro, G. (2009). Apoptosis and in vitro Alzheimer's disease neuronal models. *Communicative & Integrative Biology*, *2*(2), 163–169. https://doi.org/10.4161/CIB.7704

Cao, C., Cirrito, J. R., Lin, X., Wang, L., Verges, D. K., Dickson, A., Mamcarz, M., Zhang, C., Mori, T., Arendash, G. W., Holtzman, D. M., & Potter, H. (2009). Caffeine suppresses β-amyloid levels in plasma and brain of Alzheimer's transgenic mice. *Journal of Alzheimer's Disease : JAD*, *17*(3), 681. https://doi.org/10.3233/JAD-2009-1071

Chen, J.-F., Xu, K., Petzer, J. P., Staal, R., Xu, Y.-H., Beilstein, M., Sonsalla, P. K., Castagnoli, K., Castagnoli, N., & Schwarzschild, M. A. (2001). *Neuroprotection by Caffeine and A 2A Adenosine Receptor Inactivation in a Model of Parkinson's Disease*. http://www.jneurosci.org/cgi/content/full/5212

Chu, Y. F., Chang, W. H., Black, R. M., Liu, J. R., Sompol, P., Chen, Y., Wei, H., Zhao, Q., & Cheng, I. H. (2012). Crude caffeine reduces memory impairment and amyloid β1–42 levels in an Alzheimer's mouse model. *Food Chemistry*, *135*(3), 2095–2102. https://doi.org/10.1016/J.FOODCHEM.2012.04.148

Cornelis, M. C. (2019). The Impact of Caffeine and Coffee on Human Health. *Nutrients*, *11*(2), 416. https://doi.org/10.3390/NU11020416

Daina, A., Michielin, O., & Zoete, V. (2019). SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Research*, *47*(W1), W357–W3664. https://doi.org/10.1093/nar/gkz382

Davis, J. M., Zhao, Z., Stock, H. S., Mehl, K. A., Buggy, J., & Hand, G. A. (2003). Central nervous system effects of caffeine and adenosine on fatigue. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, *284*(2 53-2), 399–404. https://doi.org/10.1152/AJPREGU.00386.2002/ASSET/IMAGES/LARGE/H60231550004.JPEG

De Strooper, B. (2007). Loss-of-function presenilin mutations in Alzheimer disease. Talking Point on the role of presenilin mutations in Alzheimer disease. *EMBO Reports*, *8*(2), 141. https://doi.org/10.1038/SJ.EMBOR.7400897

Dixit, A. B., Banerjee, J., Tripathi, M., Sarkar, C., & Chandra, P. S. (2017). Synaptic roles of cyclin-dependent kinase 5 & its implications in epilepsy. *The Indian Journal of Medical Research*, *145*(2), 179. https://doi.org/10.4103/IJMR.IJMR_1249_14

Eskelinen, M. H., & Kivipelto, M. (2010). Caffeine as a Protective Factor in Dementia and Alzheimer's Disease. *Journal of Alzheimer's Disease*, *20*,

167–174. https://doi.org/10.3233/JAD-2010-1404

Farah, A. (2012). Coffee Constituents. *Coffee: Emerging Health Effects and Disease Prevention*, 21–58. https://doi.org/10.1002/9781119949893.CH2

Fedeli, C., Filadi, R., Rossi, A., Mammucari, C., & Pizzo, P. (2019). PSEN2 (presenilin 2) mutants linked to familial Alzheimer disease impair autophagy by altering Ca2+ homeostasis. *Autophagy*, *15*(12), 2044–2062. https://doi.org/10.1080/15548627.2019.1596489

Gardener, S. L., Rainey-Smith, S. R., Villemagne, V. L., Fripp, J., Doré, V., Bourgeat, P., Taddei, K., Fowler, C., Masters, C. L., Maruff, P., Rowe, C. C., Ames, D., & Martins, R. N. (2021). Higher Coffee Consumption Is Associated With Slower Cognitive Decline and Less Cerebral Aβ-Amyloid Accumulation Over 126 Months: Data From the Australian Imaging, Biomarkers, and Lifestyle Study. *Frontiers in Aging Neuroscience*, *13*, 744872. https://doi.org/10.3389/FNAGI.2021.744872/BIBTEX

Gene Ontology Consortium. (2017). Expansion of the gene ontology knowledgebase and resources: The gene ontology consortium. *Nucleic Acids Research*, *45*(D1), D331–D338. https://doi.org/10.1093/nar/gkw1108

Gibbs, B. F., Silva, I. G., Prokhorov, A., Abooali, M., Yasinska, I., Casely-Hayford, M. A., Berger, S. M., Fasler-Kan, E., Sumbayev, V., Gibbs, B. F., Gonçalves Silva, I., Prokhorov, A., Abooali, M., Yasinska, I., Casely-Hayford, M. A., Berger, S. M., Fasler-Kan, E., & Sumbayev, V. (2015). Caffeine affects the biological responses of human hematopoietic cells of myeloid lineage via downregulation of the mTOR pathway and xanthine oxidase activity. *Oncotarget*, *6*(30), 28678–28692. https://doi.org/10.18632/ONCOTARGET.5212

Goel, P., Chakrabarti, S., Goel, K., Bhutani, K., Chopra, T., & Bali, S. (2022). Neuronal cell death mechanisms in Alzheimer's disease: An insight. *Frontiers in Molecular Neuroscience*, *15*, 937133. https://doi.org/10.3389/FNMOL.2022.937133/PDF

Hamosh, A., Scott, A. F., Amberger, J. S., Bocchini, C. A., & McKusick, V. A. (2004). Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. *Nucleic Acids Research*, *33*(Database Issue), D514. https://doi.org/10.1093/NAR/GKI033

Huang, D. W., Sherman, B. T., & Lempicki, R. A. (2009). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nature Protocols*, *4*(1), 44–57. https://doi.org/10.1038/NPROT.2008.211

Hur, J. Y. (2022). γ-Secretase in Alzheimer's disease. *Experimental & Molecular Medicine 2022 54:4*, *54*(4), 433–446. https://doi.org/10.1038/s12276-022-00754-8

Kanehisa, M., Furumichi, M., Sato, Y., Kawashima, M., & Ishiguro-Watanabe, M. (2022). KEGG for taxonomy-based analysis of pathways and genomes. *Nucleic Acids Research*, 1–6. https://doi.org/10.1093/nar/gkac963

Kapoor, A., & Nation, D. A. (2020). Role of Notch Signaling in Neurovascular Aging and Alzheimer's Disease. *Seminars in Cell & Developmental Biology*, *116*, 90. https://doi.org/10.1016/J.SEMCDB.2020.12.011

Khezri, M. R., Ghasemnejad-Berenji, M., & Moloodsouri, D. (2023). The PI3K/AKT Signaling Pathway and Caspase-3 in Alzheimer's Disease: Which One Is the Beginner? *Journal of Alzheimer's Disease*, *92*(2), 391–393. https://doi.org/10.3233/JAD-221157/ASSET/IMAGES/10.3233_JAD-221157-FIG1.JPG

Kim, J. W., Byun, M. S., Yi, D., Lee, J. H., Jeon, S. Y., Jung, G., Lee, H. N., Sohn, B. K., Lee, J. Y., Kim, Y. K., Shin, S. A., Sohn, C. H., & Lee, D. Y. (2019). Coffee intake and decreased amyloid pathology in human brain. *Translational Psychiatry 2019 9:1*, *9*(1), 1–10. https://doi.org/10.1038/s41398-019-0604-5

Lamba, V., Winners, O., & Fort, P. (2021). Early High-Dose Caffeine Improves Respiratory Outcomes in Preterm Infants. *Children 2021, Vol. 8, Page 501*, *8*(6), 501. https://doi.org/10.3390/CHILDREN8060501

Li, R., Li, Q., & Ji, Q. (2020). Molecular targeted study in tumors: From western medicine to

active ingredients of traditional Chinese medicine. *Biomedicine & Pharmacotherapy*, *121*, 109624. https://doi.org/10.1016/J.BIOPHA.2019.109624

Liu, S. L., Wang, C., Jiang, T., Tan, L., Xing, A., & Yu, J. T. (2016). The Role of Cdk5 in Alzheimer's Disease. *Molecular Neurobiology*, *53*(7), 4328–4342. https://doi.org/10.1007/S12035-015-9369-X

Londzin, P., Zamora, M., Kąkol, B., Taborek, A., & Folwarczna, J. (2021). Potential of Caffeine in Alzheimer's Disease—A Review of Experimental Studies. *Nutrients*, *13*(2), 537. https://doi.org/10.3390/NU13020537

Louneva, N., Cohen, J. W., Han, L. Y., Talbot, K., Wilson, R. S., Bennett, D. A., Trojanowski, J. Q., & Arnold, S. E. (2008). Caspase-3 Is Enriched in Postsynaptic Densities and Increased in Alzheimer's Disease. *The American Journal of Pathology*, *173*(5), 1488. https://doi.org/10.2353/AJPATH.2008.080434

Luo, J. E., & Li, Y. M. (2022). Turning the tide on Alzheimer's disease: modulation of γ-secretase. *Cell and Bioscience*, *12*(1), 1–12. https://doi.org/10.1186/S13578-021-00738-7/FIGURES/9

Mao, H., Szafranska, K., Kruse, L., Holte, C., Wolfson, D. L., Ahluwalia, B. S., Whitchurch, C. B., Cole, L., Lockwood, G. P., Diekmann, R., Le Couteur, D., Cogger, V. C., & McCourt, P. A. G. (2023). Effect of caffeine and other xanthines on liver sinusoidal endothelial cell ultrastructure. *Scientific Reports 2023 13:1*, *13*(1), 1–13. https://doi.org/10.1038/s41598-023-40227-0

McLellan, T. M., Caldwell, J. A., & Lieberman, H. R. (2016). A review of caffeine's effects on cognitive, physical and occupational performance. *Neuroscience & Biobehavioral Reviews*, *71*, 294–312. https://doi.org/10.1016/J.NEUBIOREV.2016.09.001

Mendoza, M. F., Sulague, R. M., Posas-Mendoza, T., & Lavie, C. J. (2023). Impact of Coffee Consumption on Cardiovascular Health. *The Ochsner Journal*, *23*(2), 152. https://doi.org/10.31486/TOJ.22.0073

Nickel, J., Gohlke, B. O., Erehman, J., Banerjee, P., Rong, W. W., Goede, A., Dunkel, M., & Preissner, R. (2014). SuperPred: Update on drug classification and target prediction. *Nucleic Acids Research*, *42*(W1), 26–31. https://doi.org/10.1093/nar/gku477

Oliveros, J. C. (2024). *Venny. An Interactive Tool for Comparing Lists with Venn's Diagrams.* https://bioinfogp.cnb.csic.es/tools/venny/

Persad, L. A. B. (2011). Energy drinks and the neurophysiological impact of caffeine. *Frontiers in Neuroscience*, *5*(OCT), 12105. https://doi.org/10.3389/FNINS.2011.00116/BIBTEX

QuickGO::Term GO:0070765. (2025). https://www.ebi.ac.uk/QuickGO/term/GO:0070765

Reddy, V. S., Shiva, S., Manikantan, S., & Ramakrishna, S. (2024). Pharmacology of caffeine and its effects on the human body. *European Journal of Medicinal Chemistry Reports*, *10*, 100138. https://doi.org/10.1016/J.EJMCR.2024.100138

Research, I. of M. (US) C. on M. N., & Marriott, B. M. (1994). *Effects of Caffeine on Cognitive Performance, Mood, and Alertness in Sleep-Deprived Humans*. https://www.ncbi.nlm.nih.gov/books/NBK209050/

Rosmanah, L., Saepuloh, U., Mariya, S. S., Suparto, I. H., Manalu, W., Winarto, A., & Darusman, H. S. (2024). Expression of APP, CDK5, and AKT1 Gene Related to Alzheimer Disease in Brain of Long-tailed Macaques. *HAYATI Journal of Biosciences*, *31*(1), 145–152. https://doi.org/10.4308/HJB.31.1.145-152

Roth, K. A. (2001). Caspases, Apoptosis, and Alzheimer Disease: Causation, Correlation, and Confusion. *Journal of Neuropathology & Experimental Neurology*, *60*(9), 829–838. https://doi.org/10.1093/JNEN/60.9.829

Seppä-Moilanen, M., Andersson, S., & Kirjavainen, T. (2021). Caffeine is a respiratory stimulant without effect on sleep in the short-term in late-preterm infants. *Pediatric Research 2021 92:3*, *92*(3), 776–782. https://doi.org/10.1038/s41390-021-01794-y

Shah, K., & Lahiri, D. K. (2014). Cdk5 activity in the brain – multiple paths of regulation. *Journal of Cell Science*, *127*(11), 2391. https://doi.org/10.1242/JCS.147553

Shannon, P., Markiel, A., Ozier, O., Baliga, N. S.,

Wang, J. T., Ramage, D., Amin, N., Schwikowski, B., & Ideker, T. (2003). Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks. *Genome Research*, *13*(11), 2498. https://doi.org/10.1101/GR.1239303

Sherman, B. T., Hao, M., Qiu, J., Jiao, X., Baseler, M. W., Lane, H. C., Imamichi, T., & Chang, W. (2022). DAVID: a web server for functional enrichment analysis and functional annotation of gene lists (2021 update). *Nucleic Acids Research*, *50*(W1), W216–W221. https://doi.org/10.1093/nar/gkac194

Su, J. H., Zhao, M., Anderson, A. J., Srinivasan, A., & Cotman, C. W. (2001). Activated caspase-3 expression in Alzheimer's and aged control brain: correlation with Alzheimer pathology. *Brain Research*, *898*(2), 350–357. https://doi.org/10.1016/S0006-8993(01)02018-2

Szklarczyk, D., Kirsch, R., Koutrouli, M., Nastou, K., Mehryary, F., Hachilif, R., Gable, A. L., Fang, T., Doncheva, N. T., Pyysalo, S., Bork, P., Jensen, L. J., & Von Mering, C. (2023). The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Research*, *51*(1 D), D638–D646. https://doi.org/10.1093/nar/gkac1000

Tazzeo, T., Bates, G., Roman, H. N., Lauzon, A. M., Khasnis, M. D., Eto, M., & Janssen, L. J. (2012). Caffeine relaxes smooth muscle through actin depolymerization. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, *303*(4), L334. https://doi.org/10.1152/AJPLUNG.00103.2012

Turnbull, D., Rodricks, J. V., Mariano, G. F., & Chowdhury, F. (2017). Caffeine and cardiovascular health. *Regulatory Toxicology and Pharmacology*, *89*, 165–185. https://doi.org/10.1016/J.YRTPH.2017.07.025

Wolfe, M. S. (2012). γ-Secretase as a target for Alzheimer's disease. *Advances in Pharmacology (San Diego, Calif.)*, *64*, 127–153. https://doi.org/10.1016/B978-0-12-394816-8.00004-0

Yamaoka-Yano, D. M., Mazzafera, P., Mithico Yamaoka-Yano, D., & Mazzafera, P. (1999). Catabolism of caffeine and purification of a xanthine oxidade responsible for methyluric acids production in Pseudomonas putida L. *Revista de Microbiologia*, *30*(1), 62–70. https://doi.org/10.1590/S0001-37141999000100013

Yang, D. S., Kumar, A., Stavrides, P., Peterson, J., Peterhoff, C. M., Pawlik, M., Levy, E., Cataldo, A. M., & Nixon, R. A. (2008). Neuronal Apoptosis and Autophagy Cross Talk in Aging PS/APP Mice, a Model of Alzheimer's Disease. *The American Journal of Pathology*, *173*(3), 665–681. https://doi.org/10.2353/AJPATH.2008.071176

Zhao, Y., Zhang, L., Zhang, M., Li, S., Sun, X., Sun, X., Yao, G., Li, C., Li, M., Song, C., He, H., Jia, Y., Jv, B., Yu, Y., Zhu, Y., & Wang, L. (2024). Impact of early caffeine administration on respiratory outcomes in very preterm infants initially receiving invasive mechanical ventilation. *BMJ Open Respiratory Research*, *11*(1), 2285. https://doi.org/10.1136/BMJRESP-2023-002285

Zhou, X., & Zhang, L. (2021). The Neuroprotective Effects of Moderate and Regular Caffeine Consumption in Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity*, *2021*(1), 5568011. https://doi.org/10.1155/2021/5568011