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A Brief Review on Molecular Docking - Alzheimer's Disease

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Abstract: Alzheimer's disease (AD), a progressive brain disorder, is the most common form of dementia, affecting memory, thought, and behavior. Despite extensive research, effective therapeutic treatments for AD and dementia remain elusive. This study analyzed select transcriptomic datasets to identify disease-associated proteins meeting specific criteria. We then docked these proteins with four existing AD drugs (Donepezil, Galantamine, Memantine, and Rivastigmine) and plant-derived actives from Thymus cilicius, Melissa officinalis, Salvia sclarea, Linum usitatissimum, and Curcuma longa. Notably, binding energy values for mutant proteins differed significantly from wild-type proteins, particularly in the MET proto-oncogene (PDB ID: 3ZXZ). Moreover, plant-derived actives exhibited higher relative stability values when docked with wild-type proteins compared to conventional drugs. Our findings suggest Alpha-Muurolene, Alpha-Atlantone, Alpha-Cadinene, Beta-Bourbonene, Beta-Cubebene, and Germacrene-D as promising alternative therapeutic candidates for Alzheimer's disease.[1,2,3,11,12,13]

Keywords*: Alzheimer's Disease, Dementia, Serotonergic Receptors, Auto Dock Vina.*

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I. INTRODUCTION

Dementia is a syndrome that can be caused by a number of diseases which over time destroy nerve cells and damage the brain, typically leading to deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from the usual consequences of biological ageing. While consciousness is not affected, the impairment in cognitive function is commonly accompanied, and occasionally preceded, by changes in mood, emotional control, behaviour, or motivation.

Dementia has physical, psychological, social and economic impacts, not only for people living with dementia, but also for their carers, families and society at large. There is often a lack of awareness and understanding of dementia, resulting in stigmatization and barriers to diagnosis and care. [6,7,13,14]

➢ *Signs and Symptoms*

Changes in mood and behaviour sometimes happen even before memory problems occur. Symptoms get worse over time. Eventually, most people with dementia will need others to help with daily activities.

➢ *Early Signs and Symptoms are:*

- Forgetting things or recent events losing or misplacing things getting lost when walking or driving being confused, even in familiar places losing track of time difficulties solving problems or making decisions problems following conversations or trouble finding words difficulties performing familiar tasks misjudging distances to objects visually.
- Social interactions that stimulate the brain and maintain daily function.

Molecular docking has become a key method in drug development, enabling the prediction of ligand-protein interactions, which is essential for understanding drug efficacy. It involves determining the conformation, position, and orientation of ligands and assessing their binding affinity. Tools like Autodock Vina are commonly used, where the "force field" calculates binding energies in two steps: evaluating the interaction energies between unbound ligand and protein, and then determining the lowest interaction energies. Several studies have utilized docking for drug discovery, such as Pradeepkiran et al.'s research on alternative drug targets for Alzheimer's disease (AD), Monteiro et al.'s evaluation of flavonoids for toxicity and absorption, and Shamsi et al.'s investigation into Donepezil's interaction with human transferrin. Additionally, Saleh and Sadeghi's study highlighted the role of

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Tetrahydrodeoxycorticosterone in AD by showing how it inhibits enzyme-substrate binding through. [16,17,18,19]

II. MATERIAL AND METHODS

➢ *Gene Expression Analysis*

High-throughput gene expression data for Alzheimer's (GSE28146, GSE1297, E-MEXP-2280) and dementia (GSE5281, GSE13162) were obtained from the GEO database and analyzed using the Bioconductor platform. Differentially expressed genes were identified with thresholds of P-value < 0.05, FC < 0.5 for downregulated, and P-value < 0.05, FC > 2 for upregulated genes. Proteins corresponding to these genes were identified using the DAVID database.

➢ *Disease Protein Identification*

Proteins with PDB IDs, resolutions of 2 Å or better, at least one ligand, and classified as Homo sapiens were selected for docking studies. PDB IDs were obtained using the Biological Database Network, and 3D protein structures were sourced from PDB.

➢ *Plant and Drug Selection*

Five plants commonly used in dementia and AD treatments (Thymus cilicius, Melissa officinalis, Salvia sclarea, Linum usitatissimum, Curcuma longa) were selected. Phytochemicals from these plants were sourced from Duke's Phytochemical and Ethnobotanical Databases. A total of 117 active compounds were chosen based on molecular volume, functional groups, and matching dipole moments for docking studies. [4,5,10,11]

III. MOLECULAR DOCKING STUDIES

Molecular docking studies were performed using AutoDock Vina within the PyRx software to assess the interaction of selected compounds with AChE and BChE. PyRx, a free and user-friendly tool, facilitates docking with its intuitive interface, chemical spreadsheet functionality, and visualization capabilities, making it ideal for computer-aided drug design. The drug targets were energy minimized and converted into pdbqt format for docking analysis.

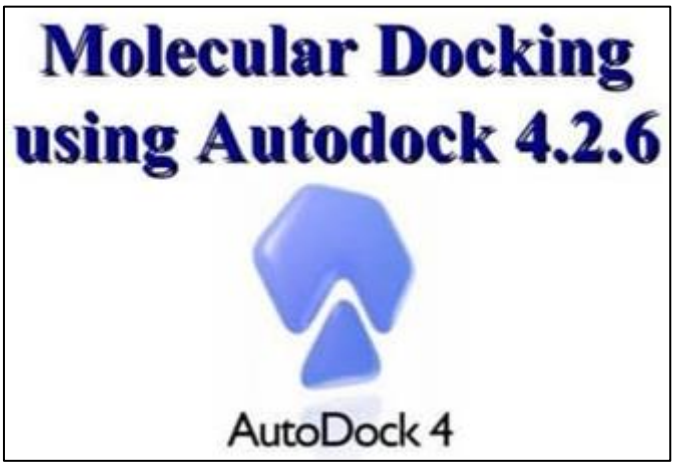

Fig 1 AutoDock Vina

➢ *Molecular Interaction Visualisation*

The docking results of protein-ligand interactions generated by AutoDock Vina were saved in PDB format and visualized using PyMOL. The visualization highlighted the ligand binding sites, surrounding amino acids, and hydrogen bond interactions between the protein and ligand. The distances of these hydrogen bonds were also calculated.

➢ *Active Site Prediction*

Active sites in proteins, where ligands or other molecules bind, were identified in AChE and BChE proteins using bioinformatics tools at IIT Delhi. These sites were visualized using the PyMOL molecular visualization software. [28]

IV. RECEPTORS INCLUDED IN ALZHEIMER'S DISEASE

There are several receptors implicated in Alzheimer's disease (AD). Some of the key receptors include:

➢ Amyloid-Beta Receptors

- NMDA receptors: Overactivation of NMDA receptors by glutamate can lead to excitotoxicity, contributing to AD.
- AMPAR receptors: Changes in AMPAR receptor composition and function have been linked to AD.

➢ *Cholinergic Receptors*

- Muscarinic receptors (M1-M5): Decreased muscarinic receptor density and function have been observed in AD.
- Nicotinic receptors: Loss of nicotinic receptors, particularly the α7 subtype, has been implicated in AD.

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➢ *Serotonergic Receptors*
- 5-HT6 receptors: 5-HT6 receptors have been identified as a potential target for AD treatment.

➢ *Other Receptors*
- ApoE receptors: Apolipoprotein E (ApoE) receptors play a role in lipid metabolism and have been implicated in AD.
- Prion protein receptors: Prion protein receptors have been linked to AD, although their exact role is still unclear.

These receptors offer potential targets for the development of new therapeutic strategies for Alzheimer's disease. [30]

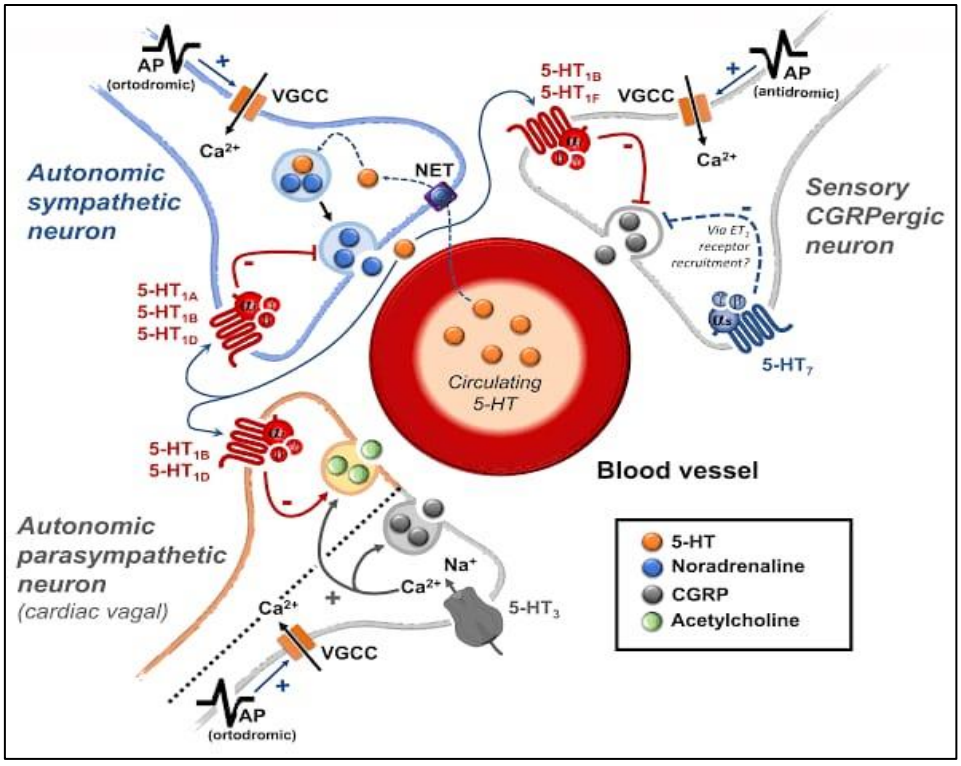

Fig 2 Seretonergic Receptors.

V. FOR ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative condition marked by progressive memory loss and cognitive decline. The pathology of AD involves the accumulation of amyloid-beta plaques, tau tangles, and a reduction in synaptic function, leading to brain cell death. Some research suggests that proteins, particularly those that can bind to receptors in the brain, may play a role in modifying or modulating these processes. Below are some proteins and their receptors that have been studied in the context of Alzheimer's. [31]

➢ *Amyloid-Beta (Aβ) and Its Receptors*
- Receptors: Amyloid-beta interacts with several cell surface receptors, including:
- Neurotrophin Receptor p75NTR (p75 neurotrophin receptor)
- N-methyl-D-aspartate)
- Low-density lipoprotein receptor-related protein 1 (LRP1)
- Mechanism: Amyloid-beta binds to the p75NTR receptor, which has been associated with neuroinflammation and cell death. Interaction with NMDA receptors may contribute to excitotoxicity, leading to neuronal damage. LRP1 is involved in amyloid-beta clearance, but dysfunctional interaction in Alzheimer's may impair this process, leading to plaque formation.

➢ *Tau and Its Receptors*
- Receptors: Tau interacts with several proteins that may contribute to its hyperphosphorylation and aggregation:
- Integrins
- Neuronal acetylcholine receptors
- Mechanism: Tau aggregation and hyperphosphorylation lead to the formation of neurofibrillary tangles. Integrin activation may alter tau's cellular dynamics, while acetylcholine receptor binding can affect tau phosphorylation, potentially influencing tau pathology.

➢ *Alpha7 Nicotinic Acetylcholine Receptor (α7 nAChR)*
- Receptors: The alpha7 nicotinic acetylcholine receptor (α7 nAChR) is implicated in cognition and neuroprotection.
- Mechanism: Activation of α7 nAChRs has anti-inflammatory effects and enhances neurotransmitter release, which is beneficial in maintaining cognitive function. In AD, dysfunction of α7 nAChRs could contribute to the neuroinflammatory processes and

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cognitive decline. Studies have suggested that α7 nAChR agonists may have potential therapeutic effects in AD by reducing inflammation and improving memory.

➢ *Sirtuins and Their Receptors*

- Receptors: Sirtuins, particularly SIRT1, interact with nuclear receptors and transcription factors.
- Mechanism: Sirtuins are involved in cellular stress resistance, repair, and aging. SIRT1 deacetylates key proteins involved in neuronal survival, including p53 and tau. It may also regulate amyloid precursor protein (APP) processing. Dysregulation of sirtuin activity could exacerbate neurodegeneration in Alzheimer's disease.

➢ *Brain-Derived Neurotrophic Factor (BDNF)*

- Receptors: BDNF binds to tropomyosin receptor kinase B (TrkB) receptors.
- Mechanism: BDNF plays a crucial role in neuronal growth, survival, and synaptic plasticity. The binding of BDNF to TrkB receptors activates intracellular signaling pathways that promote neuronal health. In Alzheimer's, reduced BDNF levels or dysfunction of its receptor signaling may contribute to synaptic loss and cognitive decline.

➢ *Apoptosis-Related Proteins (Caspases)*

- Receptors: Caspases are activated by various death receptors such as Fas and TNF receptors.
- Mechanism: Caspases play a key role in programmed cell death. In Alzheimer's, an imbalance in caspase activation may lead to excessive neuronal loss, especially in areas of the brain affected by amyloid plaques and tau tangles.

VI. POTENTIAL THERAPEUTIC TARGETS

- Targeting Amyloid-Beta: Drugs aiming to clear amyloid plaques (like monoclonal antibodies) or inhibit its formation are being explored.
- Modulating Tau: Therapies to prevent tau aggregation or enhance tau clearance are also under investigation
- Receptor Modulation: Drugs targeting α7 nAChRs, TrkB, or sirtuins may help reduce inflammation, protect neurons, or improve cognitive function. [19,20,22,25]

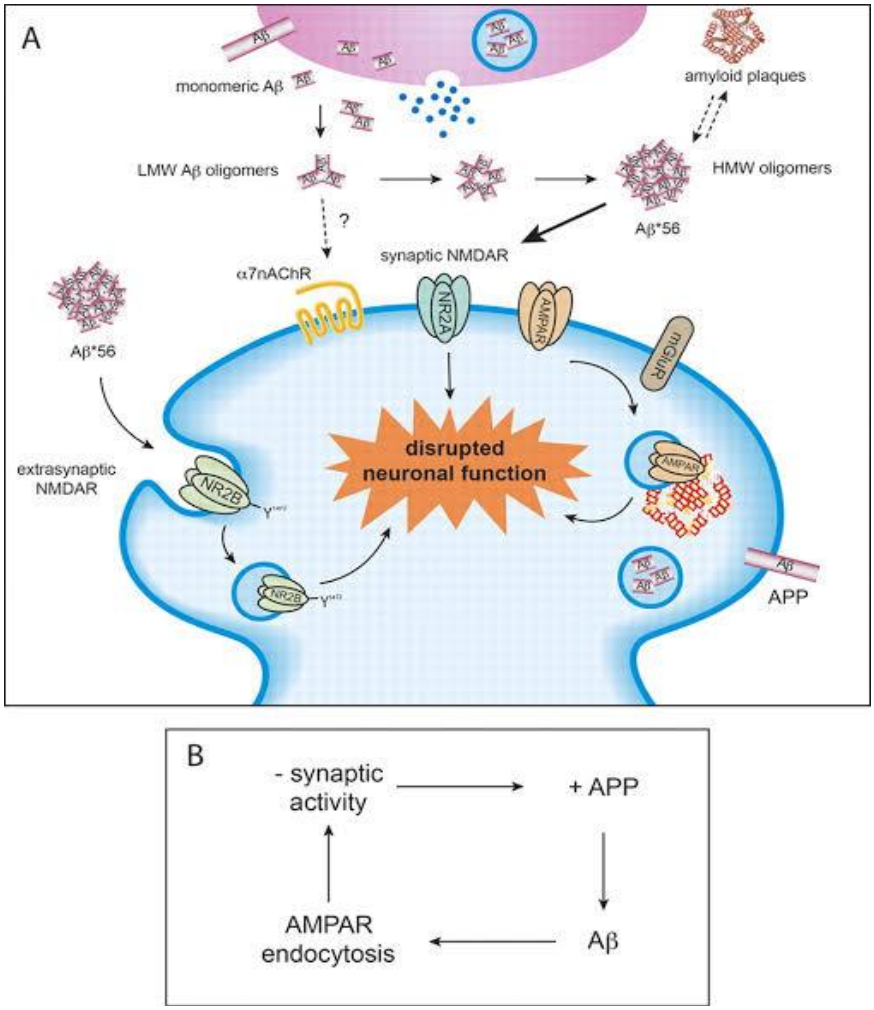

Fig 3 Amyloid Beta Receptors

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VII. CONCLUSION

In this study, docking and mutation analyses were conducted on proteins associated with dementia and Alzheimer's Disease (AD), using plant actives and drug molecules as ligands. One of the identified proteins, Phosphoglycerate Kinase 1 (PGK1), is a 417-amino acid enzyme involved in glycolysis. It is highly conserved across both prokaryotic and eukaryotic organisms, with a two-domain structure. Dysregulated glycolysis plays a significant role in the development of AD, and altered PGK1 expression can also result in conditions like muscle stiffness, hemolytic anemia, and mental retardation.

Another protein, MET (proto-oncogene, receptor tyrosine kinase), regulates vital processes like cell proliferation, morphogenesis, and survival. MET's expression is often dysregulated in various cancers and has been previously linked to AD. FKBP1B (FKBP Prolyl Isomerase 1B) is a protein involved in immunoregulation and biological processes related to protein folding and trafficking. Overexpression of FKBP1B in hippocampal neurons has been shown to potentially reverse brain aging. UBE2N (Ubiquitin-conjugating enzyme E2N) is involved in cell cycle regulation, DNA repair, and protein ubiquitination, and has been identified as a significant protein in both AD and Parkinson's Disease.

For the FKBP1B protein, docking results for Memantine showed a binding energy of -0.7 kcal/mol with the 5HKG structure. The study also investigated the binding of ligands such as pioglitazone, rosiglitazone, and tartaric acid with the ù-secretase (BACE 1) protein (PDB ID: 1sgz). Docking studies were performed separately on three chains of the BACE 1 protein as well as the complete protein, using the iGEMDOCK server. The binding energy values, summarized in a table, showed that pioglitazone exhibited the best binding affinity with the lowest binding energy compared to the other ligands, such as rosiglitazone and tartaric acid. Specifically, rosiglitazone had a binding energy of -9.79 kcal/mol, making it the most favorable ligand among the tested compounds. Binding energy serves as an initial parameter to assess the strength and affinity of the interaction between the ligand and the target protein. [8,9,14,15,18,19]

REFERENCES

[1]. Kumar A, Nisha CM, Silakari C, Sharma I, Anusha K, Gupta N, Nair P, Kumar A. Current and Novel Therapeutic Molecules and Targets in Alzheimer's Disease. J Formos Med Assoc; 2016; 115;3-10.

[2]. Selkoe DJ. Translating cell biology into therapeutic advances in Alzheimer's disease. Nature. 1999;399(6738 Suppl):A23–31.

[3]. Goedert M, Spillantini MG, Crowther RA. Tau Proteins and Neurofibrillary Degeneration. 1991;1(4):279–86. Brain Pathol.

[4]. Nunan J1, Small DH. Regulation of APP cleavage by alpha-, beta- and gamma-secretases. FEBS Lett. 2000 Oct 13;483(1):6-10.

[5]. Epis R, Marcello E, Gardoni F, Di Luca M. Alpha, beta-and gamma-secretases in Alzheimer's disease. Biosci (Schol Ed). 2012: 1;4:1126-50. Front

[6]. Hyman BT, Phelps CH, Beach TG, and others. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease, Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 2012, volume 8, issue 1, pages 1-13.

[7]. Hebert LE, Weuve J, Scherr PA and Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology, 2013. Published online before print February 6th, 2013 (DOI:

[8]. Vatanabe, I. P., Manzine, P. R., Cominetti, M. R. 2020. Historic concepts of dementia and Alzheimer's disease: From ancient times to the present. Rev Neurol, 176, 140–147.

[9]. Gale, S. A., Acar, D., Daffner, K. R. 2018. Dementia. Am J Med, 131(10), 1161-1169.

[10]. Alzheimer's Disease International, World Health Organization (WHO) Dementia: a public health priority, 2012.

[11]. Dening, T., Sandilyan, M. B. 2015. Dementia: definitions and types. Nurs Stand, 29, 37– 42.

[12]. Karantzoulis, S., Galvin, J. E. 2011. Distinguishing Alzheimer's disease from other major forms of dementia. Expert Rev Neurother, 1579-1591.

[13]. Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., Jones, E. 2011. Alzheimer's disease. Lancet, 377, 1019–1031.

[14]. Wang, J., Gu, B. J., Masters, C. L., Wang, Y. J. 2017. A systemic view of Alzheimer disease - Insights from amyloid-β metabolism beyond the brain. Nat Rev Neurol, 13, 612-313.

[15]. Jia, Y., Nie, K., Li, J., Liang, X., Zhang, X. 2016. Identification of therapeutic targets for Alzheimer's disease via differentially expressed gene and weighted gene co-expression network analyses. Mol Med Rep, 14, 4844–4848.

[16]. Moradifard, S., Hoseinbeyki, M., Ganji, S. M., Minuchehr, Z. 2018. Analysis of microRNA and Gene Expression Profiles in Alzheimer's Disease: A Meta-Analysis Approach. Sci. Rep, 8(4767).

[17]. Howes, M. J. R., Perry, E. 2011. The role of phytochemicals in the treatment and prevention of dementia. Drugs and Aging, 28, 439–468.

[18]. Rodda, J., Carter, J. 2012. Cholinesterase inhibitors and memantine for symptomatic treatment of dementia. BMJ, 344:e2986.

[19]. Yiannopoulou, K. G., Papageorgiou, S. G. 2013. Current and future treatments for

[20]. Huang, D. W., Sherman, B. T., Lempicki, R. A. 2009. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc, 4, 44–57.

[21]. Mudunuri, U., Che, A., Yi, M., Stephens, R. M. 2009. bioDBnet: The biological database network. Bioinformatics, 25, 555–556.

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14917003

[22]. Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., Bourne, P. E. 2000. The Protein Data Bank. Nucleic Acids Res, 28 235–242.
[23]. U.S. Department of Agriculture, Agricultural Research Service. 1992-2016. Dr. Duke's Phytochemical and Ethnobotanical Databases. Home Page, http://phytochem.nal.usda.gov/ http://dx.doi.org/10.15482/USDA.ADC/123927
[24]. Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B. A., Thiessen, P. A., Yu, B., Zaslavsky, L., Zhang, J., Bolton, E. E. 2019. PubChem 2019 update: Improved access to chemical data. Nucleic Acids Res, 47(D1), 11021009.
[25]. Allinger, N. L., Yuh, Y. H., Lii, J. H. 1989. Molecular Mechanics. The MM3 Force Field for Hydrocarbons. 1. J Am Chem Soc, 111(23), 85518556.
[26]. Hockney, R. W., Goel, S. P., Eastwood, J. W. 1974. Quiet high-resolution computer models of a plasma. J Comput Phys, 14, 148–158.
[27]. Allouche, A. 2012. Software News and Updates Gabedit — A Graphical User Interface for Computational Chemistry Softwares. J Comput Chem, 32, 174–182.
[28]. Valentini, G., Maggi, M., Pey, A. L. 2013. Protein stability, folding and misfolding in human PGK1 deficiency. Biomolecules, 3(4), 1030-1052.
[29]. Hipkiss, A. R. 2019. Aging, Alzheimer's disease and dysfunctional glycolysis; Similar effects of too much and too little. Aging Dis, 10, 1328–1331.
[30]. Peng, Y. S., Tang, C. W., Peng, Y. Y., Chang, H., Chen, C. L., Guo, S. L., Wu, L. C., Huang, M. C., Lee, H. C. 2020. Comparative functional genomic analysis of Alzheimer's affected and naturally aging brains. PeerJ, 8:e8682.