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Oxyberberine: A unique Tinospora cardifolia's bioactive chemical and pharmacology approach to Alzheimer's disease

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Abstract: The most common kind of dementia, Alzheimer's disease (AD), is characterised by the buildup of the proteins -amyloid protein (A42) and phosphorylated tau protein (P-tau), which causes cognitive loss and neuronal damage. Due to the limits of currently available AD medicines, other treatment agents must be investigated. Alkaloids in particular have shown potential in the treatment of neurodegenerative disorders. One of the alkaloids found in the medicinal plant Tinospora cordifolia is oxyberberine. This research uses a network pharmacology technique to look at the therapeutic mechanism of oxyberberine in AD. The positive pharmacokinetic characteristics of oxyberberine, particularly its capacity to pass the blood-brain barrier, were validated by the ADMET study. Target gene analysis identified 161 shared targets for AD and 62 common targets for oxyberberine. Oxyberberine and AD-related targets' interactions were made visible by compound-target network analysis. Ten hub genes, including MAPK1, PIK3CB, and RAC1, that are essential in the aetiology of AD were also discovered by protein-protein interaction network analysis. These hub genes were identified using gene functional enrichment analysis as being involved in important biological processes as the MAPK cascade, apoptosis control, and VEGFR signalling pathways. The findings stimulate more experimental research to confirm oxyberberine's effectiveness and fully investigate its therapeutic potential. They also provide insightful information about its possible therapeutic mechanism in AD.

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Keywords: Tinospora cordifolia, Alzheimer's disease, Network pharmacology β-amyloid protein.

Introduction:

Alzheimer's disease (AD) is widely recognised as the most prevalent form of dementia [1]. Alzheimer's disease (AD) is characterised by the presence of senile plaques, which are extracellular lesions resulting from the aggregation of β-amyloid protein (Aβ42), and neurofibrillary tangles, which are intraneuronal abnormalities consisting of phosphorylated tau protein (P-tau) [2]. It is believed that these deposits contribute to neuronal atrophy and cell death by excitotoxicity, which refers to the excessive activation of neurotransmitter receptors in neuronal membranes. This process is accompanied by disruptions in calcium homeostasis, inflammation, and the depletion of energy and brain components. Cognitive decline is seen as a consequence of the impairment of neurons and synapses responsible for memory processing, learning, and several other cognitive activities [3]. Alzheimer's disease (AD) often manifests as a progressive decline in memory and cognitive abilities, which is subsequently accompanied by a deterioration in language and visuospatial capabilities. Alterations in behaviour, such as apathy, aggressiveness, and sadness, are often linked to the aforementioned changes [4].

The worldwide population of individuals diagnosed with Alzheimer's disease (AD) presently stands at around 50 million. Projections indicate that this figure will continue to rise at five-year intervals, ultimately reaching an estimated 152 million by the year 2050 [5]. Galantamine, rivastigmine, and donepezil are often used in the management of Alzheimer's disease (AD) with the aim of decelerating its development [6]. These interventions have the potential to assist patients diagnosed with Alzheimer's disease in improving their memory, maintaining their communication skills, and managing certain impulsive behaviour patterns. However, it should be noted that these drugs possess some limitations, including restricted therapeutic efficacy and undesired side effects [7]. Therefore, it is essential to thoroughly elucidate the mechanism of Alzheimer's disease (AD) and the pursuit of secure and efficacious pharmacological interventions for AD.

Throughout history, natural products have been used for the treatment of a wide range of health issues, showcasing their significant therapeutic efficacy. Plants that include phytoconstituents have shown significant efficacy in the treatment of inflammation, neurological disorders, and their related consequences [8]. Plant secondary metabolites, like as alkaloids, flavonoids, and

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phenolic acids, play a crucial role in facilitating regeneration and inhibiting neurodegeneration [9]. Alkaloids, as a category, are a class of chemical compounds that serve as a defence mechanism in plants. They are characterised by their structural diversity and include nitrogen as a key component. Alkaloids possess significant pharmacological properties and are responsible for around 60% of drugs generated from plants. Alkaloids are present in several plant families, such as Rubiaceae, Amaryllidaceae, Fabaceae, Apocynaceae, Rutaceae, Papaveraceae, Solanaceae, and Asteraceae [10]. Alkaloids have been shown to augment the pathophysiology of neurodegenerative diseases through their inhibitory effects on enzymes such as butyrylcholinesterase and acetylcholinesterase, monoamine oxidase (MAO) inhibition, activation of muscarinic and adenosine receptors, and antagonism of N-methyl-D-aspartate (NMDA) receptors [11].

Tinospora cordifolia is a smooth, large, deciduous vine belonging to the Menispermaceae family [12-14]. The observed maximum altitude of this entity is around 300 metres, and its distribution encompasses the tropical subcontinent regions of India and China. The plant is often referred to as Giloe in the Hindi language [15]. *Tinospora cordifolia*, a plant often used in Indian Ayurvedic medicine, has shown many pharmacological effects including antioxidant, anti-aphrodisiac, anti-diabetic, and anticancer activities [16-20]. Additionally, there is evidence suggesting that an ethanolic extract of *T. cordifolia* has neuroprotective properties. This is supported by study demonstrating its efficiency in mitigating Parkinsonism produced by 6-OHDA [21]. The medicinal properties of *Tinospora cordifolia* have been attributed to its phytoconstituents, which include alkaloids, terpenoids, glycosides, sesquiterpenoids, aliphatic compounds, and steroids. The immune-modulatory and neuroprotective actions of this plant are believed to be attributed to certain alkaloids, glycosides, and aliphatic compounds [22].

Oxyberberine, also known as 8-oxyberberine, is sometimes used interchangeably and serves as a metabolite derived from berberine. Berberine (BBR) is classified as an isoquinoline alkaloid. The hydroalcoholic extract of T. cordifolia contains oxyberberine, as shown in our investigation. The hypoglycemic impact of this substance is attributed to its ability to modulate the Nrf2 and PI3K/Akt signalling pathways, as reported in reference [23]. The compound has shown potential as a promising option for the development of anticancer drugs, as shown by studies indicating its cytotoxic effects on lung and liver cell lines [24]. Based on a computer analysis of artificially produced molecules and phytochemicals present in food, it was determined that berberine had potential as a further iteration of anti-Alzheimer's disease

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therapy. Its mechanism of action involves acting as an antagonist to acetylcholinesterase in the human body [25]. Extensive study has been conducted on the therapeutic efficacy of berberine in the treatment of neurodegenerative illnesses. The compound demonstrates the ability to traverse the blood-brain barrier (BBB) when subjected to optimal physiological conditions, hence exhibiting neuroprotective properties in both cellular and animal models of Alzheimer's, Huntington's, and Parkinson's disorders [26]. Multiple studies have shown that berberine has the ability to mitigate cognitive impairment via diverse mechanisms, such as its antioxidant and anti-inflammatory properties, as well as its capacity to alleviate tau hyperphosphorylation and diminish Aβ production [27-30]. Nevertheless, there is a lack of published evidence about the neuroprotective benefits of oxyberberine in relation to Alzheimer's disease (AD).

Network pharmacology (NP) is a discipline within the field of pharmacology that integrates systems biology with multi-directional pharmacology. This study investigates the use of the multi-target approach in therapeutic interventions, as opposed to the conventional single-target methodology. Consequently, the novel approach to drug creation integrates components from computer science, molecular biology, and pharmacology. By leveraging professional networks and using various resources such as genes, proteins, illnesses, and medications, it is possible to construct a comprehensive and methodical representation of the connections between diseases, target proteins, and therapeutics [31].

The objective of this research is to identify the prominent alkaloids present in T. cordifolia and examine the pharmacological interactions among the primary active alkaloids, as well as their potential impact on Alzheimer's disease.

Methods:

The assessment of the absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics of oxyberberine was conducted in order to ascertain its appropriateness as a prospective therapeutic intervention for Alzheimer's disease. The properties under consideration were assessed.

The compound oxyberberine demonstrates compliance with the five Lipinski criteria, suggesting favourable characteristics for therapeutic development. The lipophilicity (XLOGP3) of oxyberberine was determined to be 2.94, indicating an appropriate level of lipophilicity.

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The molecular weight (MW) of oxyberberine was determined to be 351.11 g/mol. The polar surface area (TPSA) of oxyberberine was determined to be 58.92 A2. The solubility of oxyberberine was found to be favourable, as shown by a logarithmic solubility value of -3.84. The degree of unsaturation (Fraction Csp3): The degree of unsaturation of oxyberberine was determined to be 0.25. The compound oxyberberine is characterised by the presence of two rotatable bonds.

The permeability of the Blood-Brain Barrier (BBB) was assessed using the BOILED egg structure prediction model, which revealed that oxyberberine has the potential to passively traverse the BBB.

The prediction of P-glycoprotein efflux suggests that oxyberberine has the potential to be eliminated from the central nervous system.

The results obtained from the Pharmacokinetics-based Computational Screening Model (PKCSM) indicates that oxyberberine demonstrates a significant level of human intestinal absorption (HIA), with a value of 100%. The focus of this discussion is on targets. The identification of oxyberberine and its target genes in relation to Alzheimer's disease was conducted via the use of many databases, such as Swiss target prediction, Target Net, GeneCard, and DisGNet. The Swiss target prediction and Target net databases identified 107 and 475 target genes for oxyberberine, respectively. The GeneCard and DisGNet databases yielded a total of 500 target genes associated with Alzheimer's disease.
The investigation of the overlap in target genes between oxyberberine and Alzheimer's disease resulted in the identification of 62 shared target genes for oxyberberine and 161 shared target genes for Alzheimer's disease. The discovery of similar target genes shared between oxyberberine and Alzheimer's disease (AD) was facilitated by their overlapping common targets.

The compound-target network analysis was performed to visually represent the relationships between oxyberberine and its target genes that are linked to Alzheimer's disease. The network was constructed with the STRING database. The network has nodes that represent either oxyberberine or target genes, while the edges connecting these nodes symbolise their interactions. The use of color-coding for nodes and edges serves to signify the kind and intensity of interactions.

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The analysis of protein-protein interactions (PPI) networks is a crucial aspect of studying molecular biology. A protein-protein interaction network was constructed for the compound oxyberberine and its association with Alzheimer's disease, use Cytoscape software (version 3.10.1). The network facilitated the identification of the ten most significant hub genes (MAPK1, PIK3CB, RAC1, MAPK8, CDC42, MAPK9, MAP2K1, HSP90AA, PIK3CA, RPS6KB1) by the evaluation of their proximity, betweenness, and degree measures, without considering weight.

The gene functional enrichment analysis of the top 10 hub genes was conducted using the ShinyGo (version 0.76) web server. The study revealed a multitude of biological processes, cellular components, and molecular activities in which these hub genes are implicated. The findings of the study revealed many significant pathways, including Fc gamma receptor signalling, phagocytosis, MAPK cascade, apoptotic regulation, protein phosphorylation, VEGFR signalling, and stress-activated MAPK cascade.

The use of these methodologies has facilitated the attainment of a full comprehension about the possible therapeutic mechanism of oxyberberine in the context of Alzheimer's disease, as ascertained by the investigation of network pharmacology. The findings provide novel opportunities for further empirical investigations aimed at confirming the potential efficacy of oxyberberine as a viable therapeutic intervention for Alzheimer's disease.

Result:

ADMET evaluation of Oxyberberine

ADMET properties for oxyberberine showed zero Lipinski violation as it follows all five Lipinski rules. It has suitable lipophilicity (0.7<XLOGP3 (2.94) < +5.0), molecular weight (150g/mol <MW (351.11) <500g/mol), polarity (20 A^2<TPSA (58.92) <130 A^2), insolubility (-6<LogS (-3.84) <0), insaturation (0.25<Fraction Csp3 (0.25) <1) and flexibility (0<Num. rotatable bounds (2) <9). The coloured zone shown in Figure 3 demonstrates the suitable physiochemical space of oxyberberine for oral bioavailability. Figure 4 shows the BOILED egg structure for oxyberberine, which predicts that it can passively permeate through the blood-brain barrier (BBB). Moreover, the blue dot refers to oxyberberine, which is predicted to be evaluated from the central nervous system by the P-glycoprotein. PKCSM data showed that oxyberberine has high human intestinal absorption (HIA) (100%) and high BBB permeability

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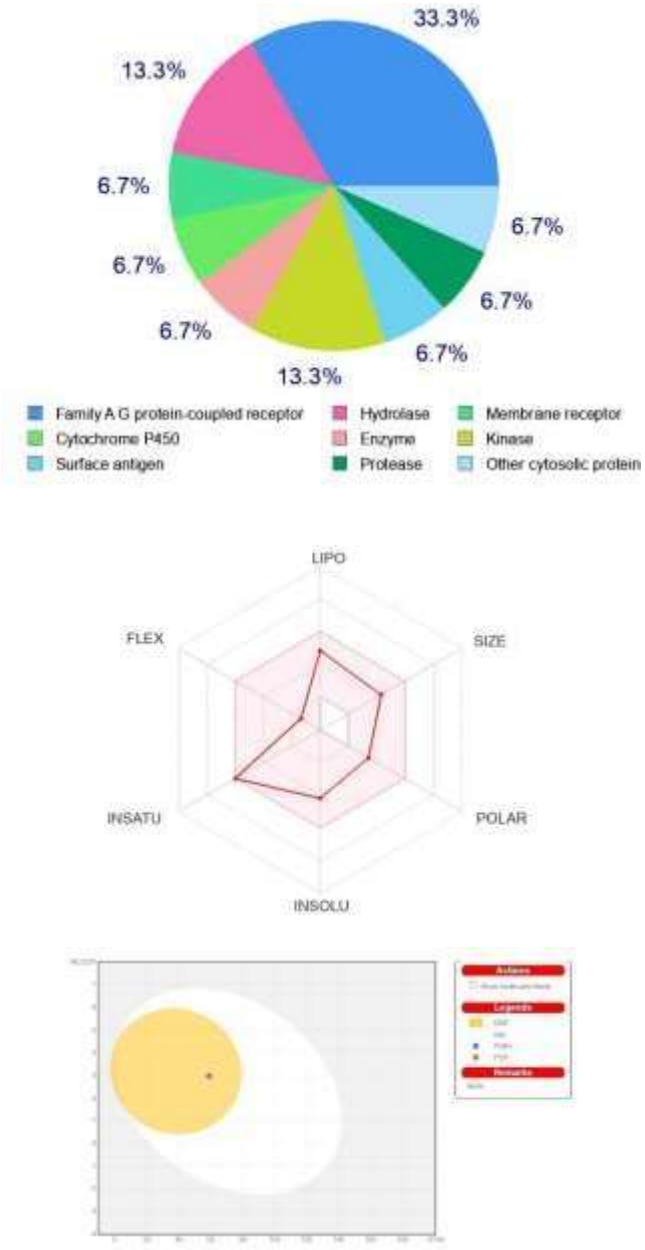

Figure 1: Targets Identification of Oxyberberine and Alzheimer's Disease

The visual representation illustrates the methodology used in identifying the specific genes linked to oxyberberine and its correlation with Alzheimer's disease. This study used the Swiss target prediction and Target net databases to identify a combined total of 107 and 475 target genes for oxyberberine, respectively. In order to identify a comprehensive collection of 500 target genes linked to Alzheimer's disease, the researchers used the GeneCard and DisGNet databases.

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The identification of common target genes for oxyberberine and Alzheimer's disease was achieved via the intersection of their respective target gene sets. This analysis revealed a total of 62 shared target genes for oxyberberine and 161 shared target genes for Alzheimer's disease. The identification of similar targets between oxyberberine and Alzheimer's disease suggests the existence of expected target genes for both entities.

The image shown depicts a critical step in understanding the potential pharmacological action of oxyberberine in the context of Alzheimer's disease. The identification of target genes hypothesised to significantly influence the therapeutic benefits of oxyberberine in Alzheimer's disease (AD) is crucial in achieving this outcome.

In contrast, the Swiss target prediction and Target net databases have shown that oxyberberine has associations with 107 and 475 target genes, respectively. A comprehensive analysis conducted by the GeneCard and DisGNet databases together revealed a total of 500 target genes that are linked to Alzheimer's disease. The Venny tool was used to ascertain the overlap of target genes associated with oxyberberine, as predicted by Swiss target prediction and target net. The present study included the examination of the intersection of target genes associated with Alzheimer's disease, as collected from the databases Genecard and Disgenet. The research's results indicated that there were a total of 62 target genes that were shared between oxyberberine and Alzheimer's disease. Additionally, the study identified 161 target genes that were uniquely associated with Alzheimer's disease. Following this, the oxyberberine targets and the targets related with the illness were overlapped in order to find common target genes.

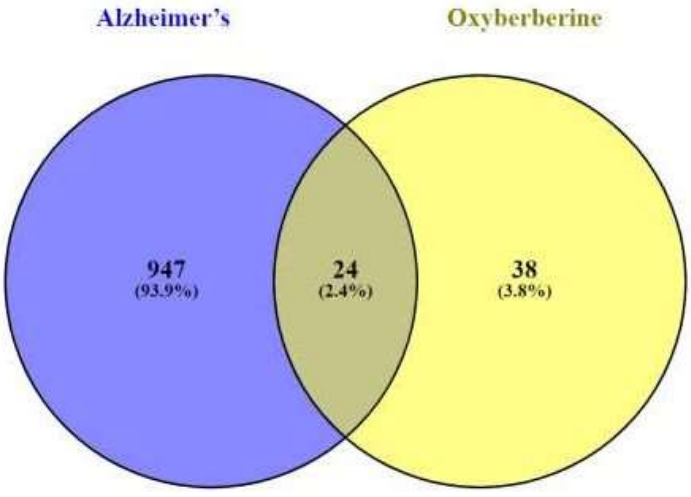

Figure 2: Compound-Target Network Analysis

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Figure 2 illustrates the network analysis conducted on the compound-target interactions involving oxyberberine within the context of Alzheimer's disease. The construction of the network was facilitated via the use of the STRING database, a valuable tool that enables the visualisation of the connections between oxyberberine and its target genes that are linked to Alzheimer's disease.

In the context of the network framework, individual nodes may be classified as either oxyberberine or a target gene, with the connections between these nodes representing their respective interactions. Distinct colours are allocated to the different nodes and edges in order to visually represent the type and strength of the interactions.

The comprehensive examination of the compound-target network provides a holistic understanding of the potential molecular interactions between oxyberberine and the target genes associated with Alzheimer's disease. The use of network analysis enables the understanding of the intricate mechanisms by which oxyberberine may induce its therapeutic effects in Alzheimer's disease (AD), while also identifying essential biological components involved in this process. The use of this methodology demonstrates its significant value in advancing the understanding of the pharmacological processes behind the possible therapeutic benefits of oxyberberine in relation to Alzheimer's disease.

The construction of the compound target network for oxyberberine and its correlation with Alzheimer's disease was carried out via the STRING database. This research demonstrates the relationship between the target genes of oxyberberine and Alzheimer's disease. The shown network has a collective count of nodes and edges, hence yielding an average node degree of. Following this, the compound-target network was submitted to the Cytoscape database for further analysis and exploration.

Protein-protein interaction (PPI) network

The construction of a protein-protein interaction network was carried out using Cytoscape (version 3.10.1) in order to examine the association between oxyberberin and Alzheimer's disease. The major objective of this database is on the identification of hub genes within the protein-protein interaction (PPI) network. The CytoNCA tool inside the Cytoscape software platform was used to ascertain the ten most significant hub genes. These hub genes were identified as MAPK1, PIK3CB, RAC1, MAPK8, CDC42, MAPK9, MAP2K1, HSP90AA, PIK3CA, and RPS6KB1. The selection of these genes was based on their closeness, betweenness, and degree measurements.

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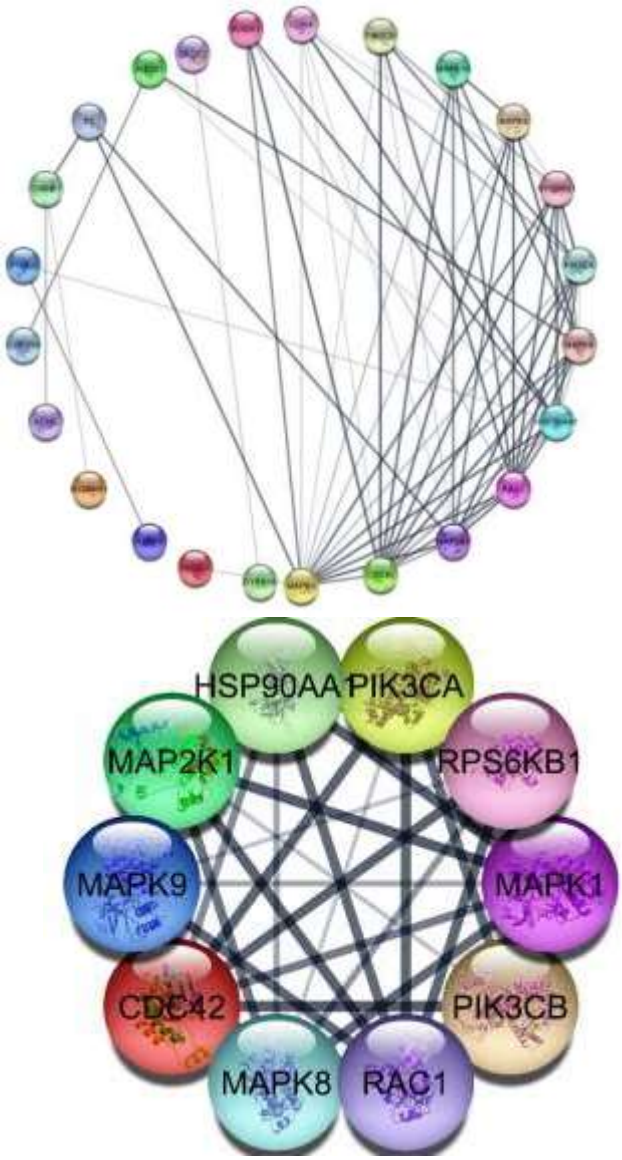

Figure 3: Gene Functional Enrichment Analysis of Hub Genes

Enrichment analysis:

The enrichment analysis demonstrated that the hub genes identified in this study are implicated in several crucial biological processes associated with Alzheimer's disease. These processes encompass cell signalling pathways such as the Fc gamma receptor signalling pathway, VEGFR signalling pathway, and MAPK cascade. Additionally, the hub genes are involved in cellular responses such as apoptotic regulation and phagocytosis, as well as protein phosphorylation. The aforementioned mechanisms play a crucial role in the pathogenesis of neurodegenerative disorders and hold promise as possible targets for therapeutic approaches.

Moreover, the investigation brought attention to distinct molecular functions, including kinase activities (such as JUN kinase activity, MAP kinase activity, and protein serine kinase activity)

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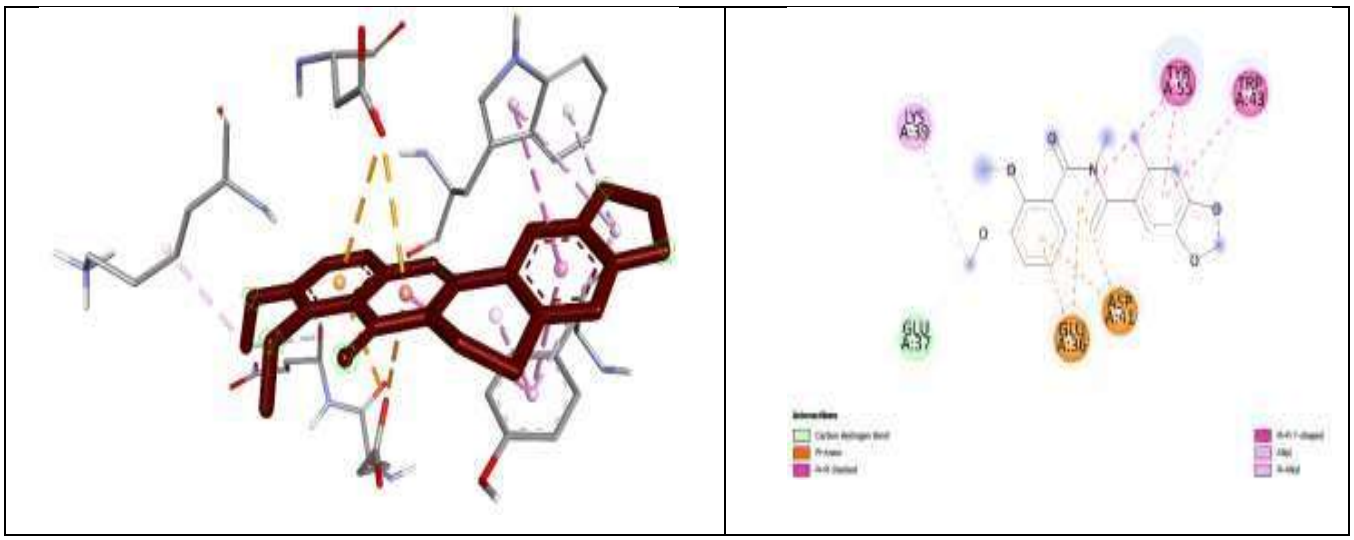
and ATP binding, which play a crucial role in cell signalling and the control of cellular processes. The identification of these molecular roles implies that the hub genes might contribute to the regulation of crucial signalling pathways implicated in the development of Alzheimer's disease.

Moreover, the research presented data about the cellular constituents linked to the hub genes, including neuronal elements such as dendrites, axons, and synapses, as well as other cellular sites such focal adhesions and anchoring junctions. Gaining knowledge about the subcellular distribution of these central genes may provide valuable insights into their involvement in neuronal processes and impairments within the framework of Alzheimer's disease. Nevertheless, the gene functional enrichment analysis provides insights into the probable molecular processes through which oxyberberine may exercise its therapeutic benefits in Alzheimer's disease. Oxyberberine has potential neuroprotective properties and may serve as a prospective option for future investigation in experimental research and drug development endeavours aimed at addressing Alzheimer's disease. This potential is attributed to its ability to target hub genes and related pathways.



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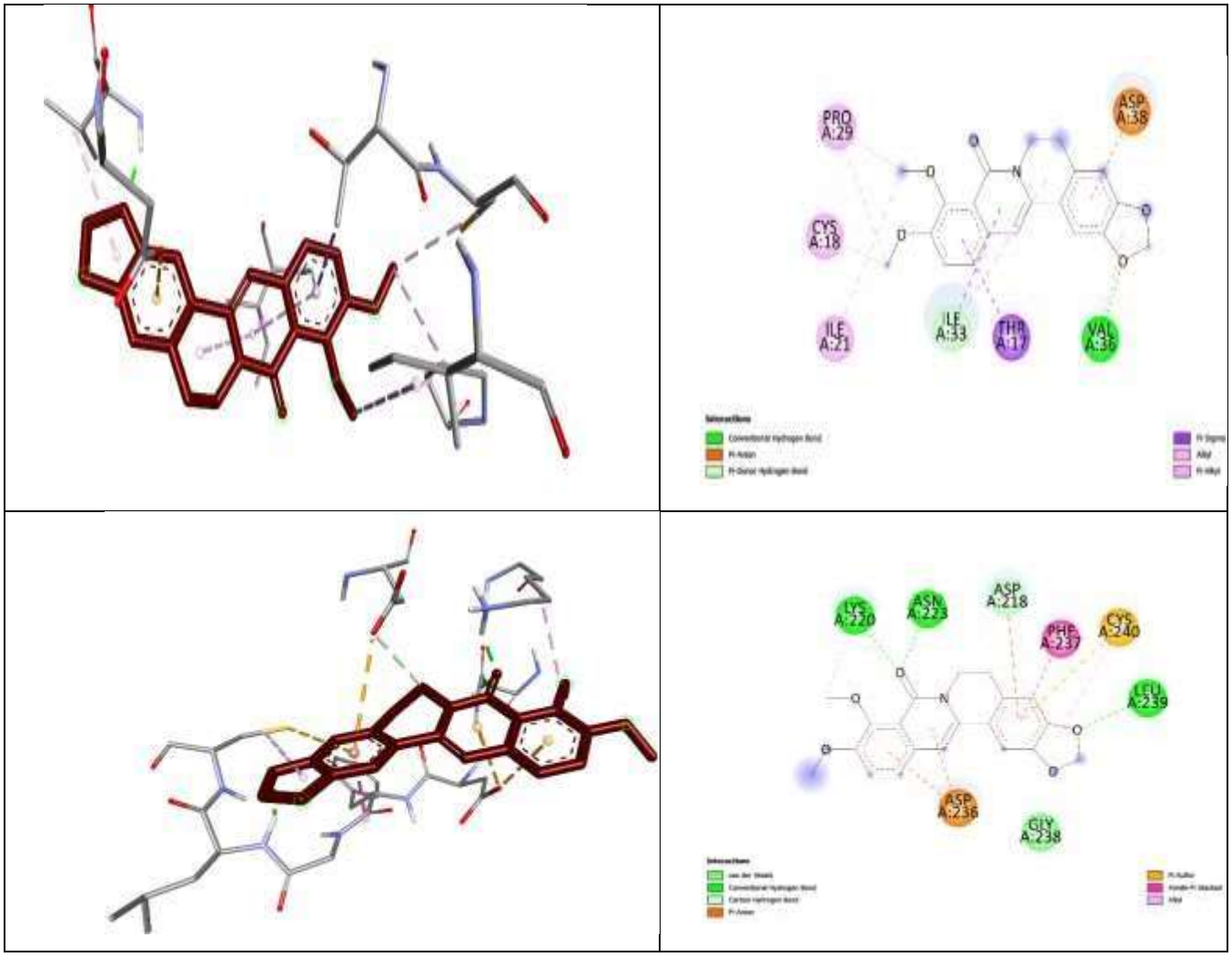
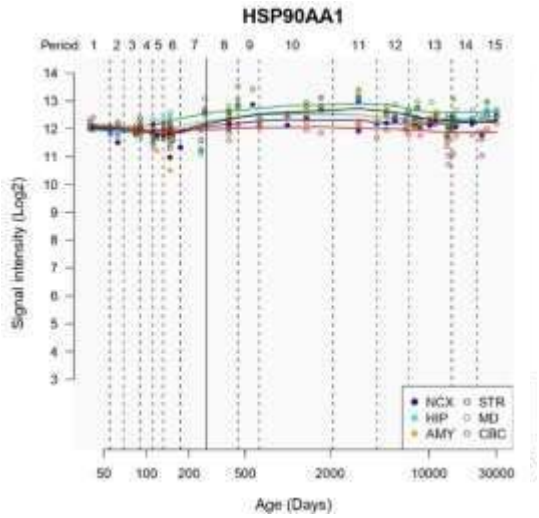
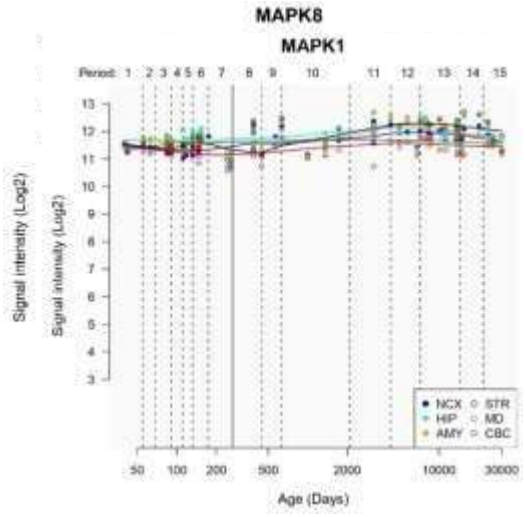


Figure 4

The Human Brain Transcriptome (HBT) dataset, accessible at https://hbatlas.org/, is a comprehensive resource that utilises Affymetrix GeneChip arrays [32-47]. The mRNA expression of PPARγ, MAPK1, STAT3, RARA, and APP remains consistent throughout the lifespan, as depicted in Figure 5. This consistency is observed across various brain regions,





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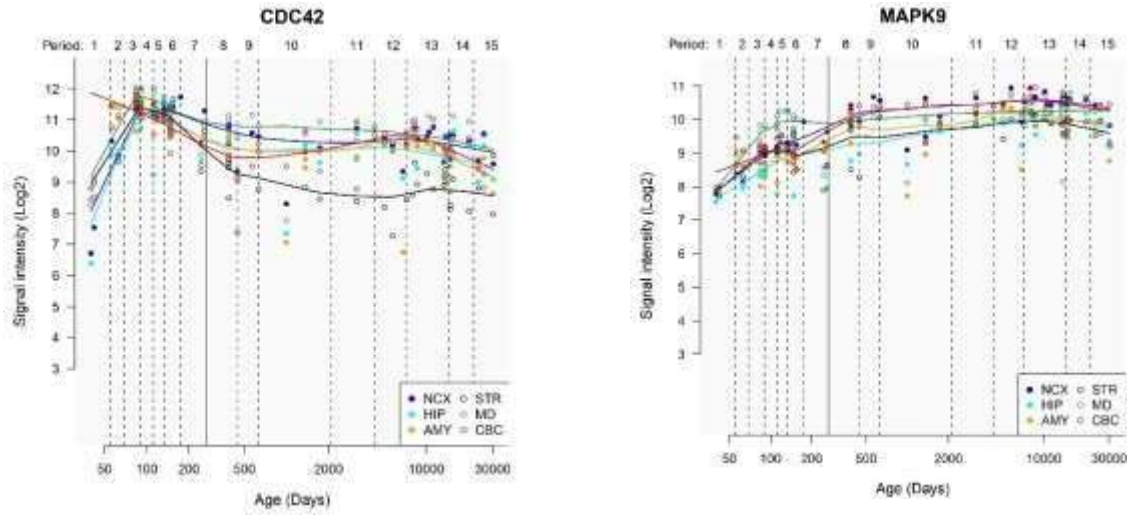
namely the mediodorsal nucleus of the thalamus (MD), cerebellar cortex (CBC), amygdala region (AMY), striatum (STR), hippocampus (HIP), and neocortex (NCX). The provided link directs to the Human Brain Transcriptome (HBT) Database.



Conclusion:

In summary, the chemical oxyberberine, which is a newly discovered bioactive substance derived from Tinospora cordifolia, has considerable promise as a therapeutic intervention for Alzheimer's disease (AD), as shown by the results acquired via the use of a network pharmacology methodology. The present work investigated the therapeutic mechanism of oxyberberine in Alzheimer's disease (AD) by the identification of its target genes and subsequent analysis of their interactions.

The pharmacokinetic qualities of oxyberberine were found to be good during the ADMET assessment, suggesting its ability to effectively penetrate the blood-brain barrier. This characteristic is particularly important for medications used to treat neurodegenerative disorders such as Alzheimer's disease. The investigation of the compound-target network revealed the connections between oxyberberine and target genes associated with Alzheimer's disease, hence emphasising the underlying molecular mechanisms that contribute to its putative neuroprotective properties.

Moreover, the elucidation of hub genes, such as MAPK1, PIK3CB, RAC1, and other relevant candidates, by the study of protein-protein interaction networks, provides valuable insights into the key molecular entities implicated in the aetiology of Alzheimer's disease. The hub genes were shown to be involved in many biological processes, including the MAPK cascade, apoptotic regulation, and VEGFR signalling pathway, which are strongly associated with the pathophysiology of Alzheimer's disease.

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The aforementioned results provide significant insights into the therapeutic mechanism of oxyberberine in the context of Alzheimer's disease. These insights suggest that oxyberberine has the potential to function as a neuroprotective agent, hence enabling the further investigation of natural products in the field of drug development. Nevertheless, more experimental investigations are necessary to substantiate the effectiveness of oxyberberine as a therapeutic intervention for Alzheimer's disease (AD) and to unveil its complete therapeutic capabilities. Hence, the research showcases the importance of network pharmacology in elucidating the intricate interplay between bioactive substances and targets associated with diseases, hence presenting a hopeful pathway for the identification of novel therapeutic interventions for Alzheimer's disease and other neurodegenerative conditions.

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