Network pharmacology and bioinformatics approach reveals the therapeutic mechanism of action of curcumin in Alzheimer disease

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Abstract
Curcumin is a natural anti-inflammatory and antioxidant substance which plays a major role in reducing the amyloid plaques formation, which is the major cause of Alzheimer’s disease (AD). Consequently, a methodical approach was used to select the potential protein targets of curcumin in AD through network pharmacology. In this study, through integrative methods, AD targets of curcumin through SwissTargetPrediction database, STITCH database, BindingDB, PharmMapper, Therapeutic Target Database (TTD), Online Mendelian Inheritance in Man (OMIM) database were predicted followed by gene enrichment analysis, network construction, network topology, and docking studies. Gene ontology analysis facilitated identification of a list of possible AD targets of curcumin (74 targets genes). The correlation of the obtained targets with AD was analysed by using gene ontology (GO) pathway enrichment analyses and Kyoto Encyclopaedia of Genes and Genomes (KEGG). We have incorporated the applied network pharmacological approach to identify key genes. Furthermore, we have performed molecular docking for analysing the mechanism of curcumin. In order to validate the temporospatial expression of key genes in human central nervous system (CNS), we searched the Human Brain Transcriptome (HBT) dataset. We identified top five key genes namely, PPARγ, MAPK1, STAT3, KDR and APP. Further validated the expression profiling of these key genes in publicly available brain data expression profile databases. In context to a valuable addition in the treatment of AD, this study is concluded with novel insights into the therapeutic mechanisms of curcumin, will ease the treatment of AD with the clinical application of curcumin.

Keywords Curcumin · Alzheimer’s disease · Network pharmacology · Key genes · Temporospatial expression

Introduction
Alzheimer's is an age-linked neurological disorder that results in progressive and irreversible cognitive impairment. It is characterized by memory loss, psychosis, and reduction in the motor skills of the affected individual caused because of the shrinkage of the brain and irreversible damage to the brain cells and their connections. The disease is prevalent in the middle-aged section of the society and especially in the United States, 5.8 million of the affected older people population is predicted to reach the 13.8 million mark by 2050 (Alzheimer’s Association 2018). The key attributes of the disease are deposits of beta-amyloid proteins called plaques and the tangles of fibers of a protein called tau (Calabrese et al. 2008). These abnormal structures are responsible for the damage and loss of connection between the nerve cells. Many pharmacological and non-pharmacological approaches have been studied to improve the symptoms and mitigate the pathological changes of AD.
Some of the approved drugs available for the treatment are popular N-methyl D-aspartate (NMDA) receptor blockers i.e., memantine, Acetyl Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) (Franchi et al. 2011). All these available therapies and drugs are designed by targeting these abnormal protein structures, or are based on the chlorogenic hypothesis and the symptoms are being targeted by them but not the pathogenesis, therefore, there is no cure for the disease developed despite the many ongoing research and clinical trials (Dou et al. 2018).

Traditional herbal medicine indigenous to India and which include Acorus calamus, Bacopa monniera, Curcuma longa, Epimedium koreanum, Ginkgo biloba, etc. are indicated as memory boosters, and some have anticholinesterase activity (Rao et al. 2012; Farooqui et al. 2018a). Turmeric, a product of Curcuma longa, a spice that has long been recognized for its medicinal properties, containing polyphenol curcumin, well known for its oxidative and inflammatory properties and its benefits in AD, besides many pharmacological actions. Curcumin or diferuloylmethane is a polyphenolic compound found in turmeric (Mehla et al. 2020). It has been reported to diminish oxidative damage and amyloid plaque formation (Lim et al. 2001; Yang et al. 2005). However, its mechanism of action in AD remains to be elucidated. Network pharmacology has emerged as an approach in advanced drug discovery and comprehending the relationship between disease and drugs at a systematic level (Berger and Iyengar 2009). In this study, we used network pharmacology to decipher target proteins linked to curcumin and elucidate the possible course of action of curcumin in AD.

Our approach is outlined in Fig. 1. Further on, by using the AD database, we can filter out five key targets involved in Aβ and tau pathology. With the help of high throughput technology and molecular docking, we verified the curcumin-related anti-AD targets.

Materials and methods

Data retrieval

Through the process of target mining and with the use of online tools viz. StringDB (v11.5) and VarElect, the targets of curcumin and the genes related to Alzheimer’s were identified. The potential anti-AD genes were selected by the intersection of these groups. Protein–protein interaction (PPI) network, Varelect database, KEGG pathway and Gene Ontology (GO) was analysed for the potential targets. The key genes obtained from the above analysis were also detected for their differential expression in other brain
regions as well. At last molecular docking was performed on the key genes observed in the PPI analysis. The work scheme is shown in Fig. 1.

Analysis of drug-likeness

Based on the Lipinski’s rule of five (RO5), drug-likenesses of the possible therapeutic compounds were observed, based on few parameters. These properties contain topological polar surface area (TPSA), molecular weight (MW), XLogP3 (water-octanol partition coefficient), hydrogen bond donor count, number of rotatable bonds, and hydrogen bond acceptor count. The other important factors of pharmacokinetics in the process of drug discovery are the brain access, bioavailability score, and gastrointestinal absorption. Bioavailability score depends on number of factors, but it depends mostly on the gastrointestinal absorption (Daina et al. 2017) (Daina and Zoete 2016). Brain Or Intestinal Estimated Prediction (BOILED-Egg) method is used for accurate prediction of this GI absorption based on the polar and lipophilic character of the small molecules (Daina and Zoete 2016).

Curcumin’s SMILES format (COClC = CC(= C(1) C = CC(= O)CC(= O)C = CC2 = CC(= C(= C2)O)OC)O was downloaded from the PubChem database (pubchem.ncbi.nlm.nih.gov) and uploaded into the Swiss-ADME server (http://www.swissadme.ch/), a web-based tool to access the bioavailability, gastrointestinal absorption and drug-likeness of the small molecules (Daina et al. 2017) (Abdul-Hammed et al. 2022).

Predicting targets of curcumin

The Potential Targets were collected from SwissTargetPrediction databases (http://www.swisstargetprediction.ch/) server (Daina et al. 2017), STITCH database (http://stitch.embl.de/), BindingDB (https://www.bindingdb.org/bind/index.jsp) (Liu et al. 2007) and The PharmMapper (http://lilab.ecust.edu.cn/pharmmapper/) server (Wang et al. 2017) on 22 Jun 2021. The predicted targets were obtained by using the SMILES format of curcumin in BindingDB and Swiss Target Prediction database, based on the principles of structural similarity. The compound’s name (Curcumin) was used to search the targets in STITCH database (Kuhn et al. 2012). Moreover, curcumin’s structure file (PubChem CID: 969,561) was imported into PharmMapper server, for downloading possible targets by applying the pharmacophore mapping method. For the normalization of the derived targets, UniProt Database was used (http://www.uniprot.org/). Next, the potential target proteins derived from various sources were integrated and redundant targets were eliminated. Finally, a total of 376 targets genes were collected from different databases after merging and removing redundant genes. This gene set was called “targets of curcumin”.

Collecting targets related to Alzheimer’s disease

To certify the complete collection of the disease-associated genes, AD-related targets were retrieved from Therapeutic Target Database (TTD, http://bidd.nus.edu.sg/group/cjttd/), Comparative Toxicogenomics Database (http://ctdbase.org/), Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org/), and CooLGeN database (http://cjttd.embl.de/) on 23 Jun 2021. In the source database used, the above phenotype keyword ‘Alzheimer’ was set. The target proteins having hit scores of 5 and more were identified as AD-associated genes from the CooLGeN database (Yang et al. 2020). The set of a gene called “genes of AD” containing 495 genes was finalised after merging the collected genes and removing redundant data. The convergence of the above two sets of targets protein scan be possible anti-AD targets of curcumin.

Phenotypic-genotypic correlation analysis

The VarElect is a free-online phenotype-dependent database that allows for effective screening and rapid prioritization of direct and indirect associations between genes and diseases (Stelzer et al. 2016; Barshir et al. 2021). The online VarElect tool was used on 10 August 2021, to perform the correlational analysis between the “anti-AD targets” and the phenotype of “AD”. The main role of VarElect analysis tool is its ability to perform gene list elucidation and scoring on the basis of phenotypic keywords, entered by the user (Chen et al. 2019). The scoring method used in VarElect was derived basically from Elasticsearch technology (Kononenko et al. 2014). The score of a specific phenotype is determined by its recurrence in the individual Genecards database, in comparison to the scores in all genes (Chen et al. 2019).

Protein–protein interaction network construction and analysis

Protein–Protein Interaction (PPIs) are substantial for the comprehension of individual protein functions and complex cellular pathways that are associated in the development of diseases (Ding and Kihara 2019). Upon following the latest studies, PPIs are related to many diseases like cancer, AD and many other neurodegenerative diseases and do have the potential to act as a promising strategy for the drug design and artificial designing of proteins (Lu et al. 2020). Protein–protein interaction network mapping was done on common genes of Curcumin and AD, and the closely related genes were analysed using GeneMANIA database (https://genemania.org/) with the species limited to “Homo sapiens”. The PPI network was built using Cytoscape (version 3.6.1) which is employed for the integration and visualization of the data (Shannon et al. 2003). Network topological
properties like the degree, betweenness, and closeness centrality were analysed making use of Network Analyzer a plugin of Cytoscape.

**Topological properties of the network**

Topological analysis helps to understand a network's structure, which makes it easy to understand and elucidate the hidden mechanisms (Ali et al. 2018). The centrality measurement of the PPI network of AD associated genes are defined by betweenness ($C_B$), and closeness ($C_C$). Using Network Analyzer (Assenov et al. 2008), the centrality measurements were calculated. These topological parameters were used to monitor the topological changes that occurred with network perturbation. In order to investigate the essential behaviours of the network, the following network properties were analysed.

**Degree**

During the network analysis, the total number of links established by a node in the network is called degree and indicated by $k$. In the process of network regulation, it is considered as measure of the local significance of a node. The graph is depicted by $G = (N, E)$, where $E$ denotes the edges while the nodes are denoted by $N$.

$C_B$ and $C_C$ are the basic parameters and centrality measures for the approximation of global functional significance of node in a network regulation (Newman and Girvan 2004).

**Betweenness centrality**

It is a measure of the extent of speed of communication of a node among other pairs of nodes in the network. This nodal measure $c_B(u)$ is calculated as the number of shortest path-path traffic from all possible routes passing through a node $u$ (Equation 1).

$$c_B(u) = \sum_{v \in E \neq u} \frac{\sigma_{uv}(u)}{\sigma_{vw}}$$  \hspace{1cm} (1)

The betweenness centrality is the parameter of the capability of a node to extricate benefit from the information flow all through the network (Brandes 2001) and its capability to control the signal processing over the other nodes through the network (Newman and Girvan 2004).

**Closeness centrality**

It measures closeness of a node from the other nodes in a network i.e., how short a path is. The nodal measure $c_C(u)$ is calculated as the inverse of the sum of distances between the node of interest $u$ and all other $v \in V \setminus u$ (Equation 2).

$$c_C(u) = \frac{1}{\sum_{v \neq u} d(u, v)}$$  \hspace{1cm} (2)

Closeness centrality depicts the speed of information distribution within a network i.e. from one node to other connected nodes (Assenov et al. 2008). The function of the node depends upon the neighbour’s centralities and changes in accordance to the types of network association. There are very few chances that the node remains isolated in such closely connected node regions. Thus, it is an influential indicator of information conveyance source of a node within a network (Farooqui et al. 2018b).

**Gene ontology enrichment analysis of core targets genes**

The Gene Set Enrichment Analysis (GSEA) is a powerful analytical tool which is used for elucidating gene expression data which was generated by genome-wide experiments. These enrichment analyses tools help to connect previous knowledge to newly generated data and therefore discover the nature of genes in the conditions of health and disease (Subramanian et al. 2005; Tipney and Hunter 2010). The Enrichr tool was used for the KEGG and GO analysis for the targets predicted against AD. Enrichr is an extensive web server for enrichment analysis and annotation of gene. It consolidates various databases like KEGG, GEO, GO, PPI databases, ChEA 2016, OMIM, etc. (Kuleshov et al. 2016). Another comprehensive database called Metascape was used exclusively for the enrichment analysis. It is a tool, used to perform multi-platforms OMICs data interpretation and analysis (Zhou et al. 2019). To perform the enrichment analysis and gene annotation, the following steps were taken: Primarily, the curcumin related anti-AD gene list was input into the Enrichr and Metascape web server. Next, the information about the signalling pathway was selected on the basis of the clinical and the pathological data.

**SynGO gene ontology**

On the basis of neurobiological and genetic evidence, the abnormally regulated synaptic genes are considered responsible for the aberrant brain plasticity which in turn is the convergent factor of brain disorders like Autism, Parkinson’s and Alzheimer’s disease (Monday and Castillo 2017). SynGO is a global, publicly available database which is used for synapse research, analysis and elucidation of omics data on a large scale. The large number of genes present on this database which are highly enriched amidst the genes related to brain disorders. This database contains exclusive annotations based on expert-curated and published information (Koopmans et al. 2019). The list of anti-AD genes was imputed into the SynGO online database and visualization.
tool to analyse and evaluate function and locations of synaptic genes to perform enrichment studies.

**Validation of spatiotemporal expression patterns of five key gene in various regions of human brain**

We identified the expression pattern of RARA, APP, PRARG, STAT3 and MAPK1 in various tissues of brain and developmental stages using BRAINEAC (www.brain-eac.org/). It is a large exon-specific eQTL database covering ten different regions of brain obtained from 134 post-mortem brains of the people belonging to European descent without any brain disorders. This database was used to inspect spatial dynamics of RARA, APP, PRARG, STAT3 and MAPK1 expression in all covered brain regions. BRAINEAC database was accessed on 30 October 2021 to conduct e-QTL analysis. The data of this database was derived from MRC Sudden Death Brain Bank in Edinburgh, UK and the Sun Health Research Institute, which includes 10 regions of the brain (temporal cortex, hippocampus, medulla, putamen, occipital cortex, thalamus, intralobular white matter, substantia nigra, frontal cortex, and cerebellum) (Sng et al. 2019).

**Molecular docking active components**

To evaluate the strength and the mode of interaction between the key proteins obtained and the curcumin molecule, the molecular docking was performed. This helped us to obtain deep understanding of the mechanism of action between the curcumin and the key target protein. The molecular docking was conducted by the Glide tool from Schrodinger maestro. Glide makes use of chain of hierarchical filters to find probable positions of the ligand in the active-site region of the receptor and provides superior robustness in the binding mode prediction (Friesner et al. 2004). The protein crystal structure was acquired by the Protein Data Bank (https://www.rcsb.org) database. Then the protein was prepared to remove the waters and any other associated molecules. The 3D structure of the ligand was downloaded in the SDF file from the PubChem Database. Finally, the ligand docking was done using Glide tool. The binding energy and the mode of interaction were studied after that.

**Results**

**Molecular properties of curcumin**

The Lipinski rule of five (RO5) establish pharmacokinetic properties of drugs such as distribution, metabolism, absorption, and excretion on specific molecular properties. In accordance with RO5, the potential compound’s molecular weight should be at most 500 Dalton, the rotatable bond below 10, the hydrogen bond acceptors below 10, and the hydrogen bond donors below 5, calculated (XLogP3-AA) octanol/water partition coefficient (XLogP3-AA) of no more than 5 and Polar surface area (PSA) no more than 140 Å². Our results indicated that our results were in accordance with RO5, 0.55 Bioavailability score and High gastrointestinal absorption showing that curcumin has good drug-like properties without any violations (Table 1). The drugs with bioavailability score 0.55 or more have good pharmacokinetic properties and are considered potential candidates for oral drugs (Bojarska et al. 2020).

**Analysis between targets of curcumin and AD**

In this study, the targets of the curcumin were predicted using the STITCH, the Binding DB, the PharmMapper and Swis sTargetPrediction databases. After merging target proteins obtained, 383 targets for curcumin were obtained. Additionally, AD-linked genes were retrieved from the OMIM, CTD, TTD, and CoolGeN databases. 512 targets were obtained after redundant data were deleted. Finally, 74 genes were selected from the intersection of the curcumin targets and AD targets. A drug exhibits characteristics called as poly pharmacology or drug promiscuity which means it can bind to multiple targets. Thereby, it is important to understand the drug-target interactions. To study the relationship between curcumin and the targets, a compound-target network (C-T network) was built. This network had 75 nodes and 74 edges and is presented in Fig. 2.

**Gene enrichment analysis**

We conducted KEGG pathway and GO enrichment analyses to expound the potential biological functions of 74 target genes. GO annotation and KEGG pathway analyses for the 74 targeted genes were performed. The significant enrichment of these targeted genes are shown in Fig. 3. The targeted gene was enriched in molecular function (MF) including

| Table 1 Curcumin’s molecular properties |
|----------------------------------------|
| Property                  | Value                |
|---------------------------|----------------------|
| Molecular Weight          | 368.38 g/mol         |
| XLogP3-AA                 | 3.20                 |
| PSA                       | 93.06 Å²             |
| Rotatable Bonds           | 8                    |
| H-bonds donor             | 2                    |
| H-bonds acceptor          | 6                    |
| Molar refractivity         | 102.80               |
| Bioavailability Score     | 0.55                 |
| GI Absorption             | High                 |
| Blood Brain Barrier Permeability | No                  |
transmembrane receptor protein kinase activity, the transition of metal ion binding, MAP kinase activity, etc. (Fig. 3A). As for cellular component the targeted genes are involved in the dendrite, neuron projection, axon, nucleus, intracellular organelle lumen, etc. (Fig. 3B). According to the GO enrichment results these targets not only regulate Protein phosphorylation, transferase activity, inflammatory response and peptidyl-tyrosine modification (Fig. 3A) but also regulate the Protein kinase binding, Protein homodimerization activity and DNA binding (Fig. 3C). As shown in these Fig. 3C top 10 terms in biological process and Molecular process were related to “protein phosphorylation” (GO: 0,006,468), regulation of “inflammatory response” (GO: 0,050,727) and regulation of “kinase activity” (GO: 0,043,549). All these are mainly related to development and spread of the AD.

Additionally, the pharmacological mechanism of the curcumin against the AD was studied using the KEGG analysis using the Enrichr tool and DisGeNET analysis using the Metascape online database. After the enrichment analysis of the pathway 74 genes were mapped to 171 pathways. The results showed that many targets played role in multiple biological pathways simultaneously. For example, both curcumin targets and AD related targets. (D) Interaction network of genes targeted by curcumin.

Fig. 2 (A) Molecular action of curcumin in the Alzheimer’s disease (AD). (B) Curcumin targeted genes and their role pathway of different diseases. (C) 74 genes selected from the intersection of group of...
KDR and MAPK1 were both involved in the Ras signalling pathway (Fig. 3D and E). It has been studied further that the activation of the Ras-ERK signalling is responsible for the hyperphosphorylation of the tau proteins another major hallmark for the AD (Kirouac et al. 2017). The results indicated that the curcumin could have therapeutic effect against AD through targeting various pathways and proteins.

PPI network of the potential targets of curcumin against Alzheimer disease and key gene identification

Using the GeneMANIA database, PPI networks were built, visualized, and analysed by cytoscape software. The PPI data and network is shown in Fig. 4A. Network Analyzer (cytoscope plugin) was utilized to analyse the network topological properties. (Supplementary file 1). Here, the highest degree is 99 and the lowest degree is 1. To quantify and visualize the relation between the genes and understand the functions of proteins at the systematic level the PPI network was obtained. The data was then analysed based on the topological parameters like betweenness, degree, and closeness and then it was found that APP was present in the center of the network having the largest degree (degree = 53), closeness (closeness = 0.699), and betweenness (betweenness = 0.06) followed by MAPK1, PPAR γ, STAT3, CTSD, AGTR1, RARA, MET, STAT1, and KDR. A gene with a higher degree (k) and centralities (betweenness and closeness) value can aid to recognize a biological system having a main role in the network. Therefore, we have computed degree (k), centralities betweenness (CB) and closeness (CC) by using NetworkAnalyzer. The details of the top ten degrees and centrality measurement (CB and CC) of PPI network are given in Fig. 4B, C and D respectively. First, we have selected the first 10 genes based on the ranking of degree, betweenness and closeness. After that find, the common genes in degree, betweenness, and closeness of network (Fig. 4E). We identified key genes in the regulatory network of AD. Therefore, we have identified five key genes RARA, APP, PRARG, STAT3 and MAPK1 in the PPI network (Fig. 4A).
These entire key genes play a great role in the progression of AD. The PPI network of 74 genes is shown in Fig. 4A with the key gene highlighted in yellow. The regulatory network of these key genes is given in Fig. 4F. These newly discovered key proteins may be beneficial as therapeutic targets.

**Mapping of targeted AD genes with all brain expressed genes analysis**

SynGO (Koopmans et al. 2019) showed clear enrichment in ontological categories correlated with synaptic signalling and synapse organisation for inhibitory neuron genes found with AD-targeted genes. The evaluation of the results indicated that 15 genes like CTSD, APP, and MAPK1 are synaptic and are localised in the synaptic membrane. 10 genes are presynaptic and are localised in the pre-synaptic membrane, endosome, cytosol and exoskeleton. Out of the inputted genes, 16 genes were also showing a role in process of synapse. Studies have also established that CTSD and APP protein promotes synapse formation and neuronal migration. The impairment of CTSD and APP protein can lead to dysregulation of synaptic transmission, therefore, the protein has a part in the pathophysiology of cerebral degenerative disease (Niemeyer et al. 2020; Hefter et al. 2020). Figure 4G below shows the biological function of genes in the synapses.

**VarElect analysis of the key genes**

For the genotypic-phenotypic analysis of 74 intersection genes were loaded in the VarElect online server. The result is shown in Table 2. Amyloid precursor protein (APP) is a single-pass transmembrane protein belonging to the family of the proteins called amyloid precursor-like proteins (APLP) in Drosophila, APLP1, and APLP2 of mammals. This APP protein is responsible for the lodgement of the neurotoxic β-amyloid peptide (Aβ) in the brain which is the key factor for the development of AD (O’Brien and Wong 2011). In humans, the APP gene is present on chromosome number 21 which translates into three isoforms i.e., APP695, APP770, and APP751. These forms vary based on the

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**Fig. 4** The PPI network of targets of curcumin against Alzheimer’s disease: (A) PPI network of genes targeted by curcumin which is associated in AD. (B) The bar graph of top 10 hub genes. (C) top 10 ranked genes selected from Betweenness centrality. (D) top 10 ranked genes selected from Closeness centrality. (E) Common genes of top 10 high rank among degree, Betweenness, Closeness centrality. (F) Regulatory network of five key genes targets of curcumin in Alzheimer’s disease. (G) Sunburst plots depict synaptic locations starting with the synapse (centre), postsynaptic and presynaptic locations in the first ring and child terms in subsequent rings. The significant SynGo biological function of 74 genes selected from the intersection of group of curcumin targets and AD related targets of SynGo.
## Table 2: VarElect Analysis of target proteins of Alzheimer with the targets of Curcumin. The score tells the relation between the genes and the target phenotype

| Symbol | Description | Category | Score | Average Disease-Causing Likelihood |
|--------|-------------|----------|-------|-----------------------------------|
| APP    | Amyloid Beta Precursor Protein | Alzheimer | 41.00 | 77.65% |
| PLAU   | Plasminogen Activator, Urokinase | Alzheimer | 28.26 | 32.24% |
| NOS3   | Nitric Oxide Synthase 3 | Alzheimer | 28.26 | 58.50% |
| GBA    | Glucosylceramidase Beta | Alzheimer | 13.62 | 61.31% |
| BACE1  | Beta-Secretase 1 | Alzheimer | 6.81 | 78.70% |
| GS3KB  | Glycogen Synthase Kinase 3 Beta | Alzheimer | 6.11 | 83.18% |
| MAOB   | Monoamine Oxidase B | Alzheimer | 5.67 | 84.51% |
| PPARA  | Peroxisome Proliferator Activated Receptor Alpha | Alzheimer | 5.56 | 36.99% |
| CTSD   | Cathepsin D | Alzheimer | 5.52 | 68.84% |
| PPARy  | Peroxisome Proliferator Activated Receptor Gamma | Alzheimer | 5.50 | 58.38% |
| TTR    | Transthyretin | Alzheimer | 5.32 | 43.90% |
| MME    | Membrane Metalloendopeptidase | Alzheimer | 5.26 | 69.79% |
| AKT1   | AKT Serine/Threonine Kinase 1 | Alzheimer | 5.15 | 90.77% |
| IL2    | Interleukin 2 | Alzheimer | 5.12 | 75.55% |
| HTR7   | 5-Hydroxytryptamine Receptor 7 | Alzheimer | 5.12 | 82.77% |
| ESR1   | Estrogen Receptor 1 | Alzheimer | 5.12 | 68.53% |
| CASP3  | Caspase 3 | Alzheimer | 5.12 | 64.18% |
| MAPK8  | Mitogen-Activated Protein Kinase 8 | Alzheimer | 5.09 | 87.00% |
| MAPK10 | Mitogen-Activated Protein Kinase 10 | Alzheimer | 5.09 | 78.02% |
| HMOX1  | Heme Oxygenase 1 | Alzheimer | 5.09 | 31.92% |
| CDK1   | Cyclin Dependent Kinase 1 | Alzheimer | 5.06 | 79.71% |
| MAPK1  | Mitogen-Activated Protein Kinase 1 | Alzheimer | 5.06 | 73.83% |
| CDK5R1 | Cyclin Dependent Kinase 5 Regulatory Subunit 1 | Alzheimer | 5.06 | 88.63% |
| ALOX5  | Arachidonate 5-Lipoxygenase | Alzheimer | 5.06 | 77.22% |
| CYP19A1| Cytochrome P450 Family 19 Subfamily A Member 1 | Alzheimer | 5.06 | 49.30% |
| PTGS2  | Prostaglandin-Endoperoxide Synthase 2 | Alzheimer | 5.06 | 66.54% |
| REG1A  | Regenerating Family Member 1 Alpha | Alzheimer | 5.06 | 82.07% |
| HMGCR  | 3-Hydroxy-3-Methylglutaryl-CoA Reductase | Alzheimer | 5.06 | 83.06% |
| REN    | Renin | Alzheimer | 5.06 | 75.65% |
| INSR   | Insulin Receptor | Alzheimer | 5.06 | 75.63% |
| NOS2   | Nitric Oxide Synthase 2 | Alzheimer | 5.06 | 46.59% |
| EPHA1  | EPH Receptor A1 | Alzheimer | 2.93 | 34.44% |
| AGTR1  | Angiotensin II Receptor Type 1 | Alzheimer | 2.60 | 63.82% |
| ADH1C  | Alcohol Dehydrogenase 1C (Class I), Gamma Polypeptide | Alzheimer | 2.05 | 0.00% |
| S100A9 | S100 Calcium Binding Protein A9 | Alzheimer | 1.69 | 67.27% |
| HTR1A  | 5-Hydroxytryptamine Receptor 1A | Alzheimer | 0.72 | 56.88% |
| MAOA   | Monoamine Oxidase A | Alzheimer | 0.62 | 84.12% |
| DRD4   | Dopamine Receptor D4 | Alzheimer | 0.62 | 0.00% |
| HSP90AA1| Heat Shock Protein 90 Alpha Family Class A Member 1 | Alzheimer | 0.51 | 79.59% |
| ESR2   | Estrogen Receptor 2 | Alzheimer | 0.51 | 54.14% |
| MMP9   | Matrix Metalloproteinase 9 | Alzheimer | 0.36 | 20.28% |
| PARP1  | Poly(ADP-Ribose) Polymerase 1 | Alzheimer | 0.36 | 45.76% |
| PDE5A  | Phosphodiesterase 5A | Alzheimer | 0.36 | 29.70% |
| ALB    | Albumin | Alzheimer | 0.36 | 82.33% |
| SOD2   | Superoxide Dismutase 2 | Alzheimer | 0.36 | 35.48% |
| NFE2L2 | Nuclear Factor, Erythroid 2 Like 2 | Alzheimer | 0.36 | 54.66% |
presence of Kunitz Protease Inhibitor (KPI) domain within their extracellular regions (Kang and Müller-Hill 1990). The APP695 lacks this domain and it has been reported that in AD patients this KPI lacking isoform gets converted to KPI containing isoforms i.e. APP770 and APP751 which is found associated with increased production of Aβ (Bordji et al. 2010). Another Protein called Cathepsin D (CTSD) is a gene that is involved in the processing of APP protein. The impaired activity of the CTSD protein leads to the accumulation of the β-amyloid peptide (Aβ) thereby causing the progression of AD (Di Domenico et al. 2016)(Schuur et al. 2011). The development of the amyloid peptides causes an inflammatory response in the brain. The peroxisome proliferator-activated receptor gamma (PPAR-gamma) is a transcription factor which suppress that inflammatory gene expression by regulating glucose and lipid metabolism (Tyagi et al. 2011)(Govindarajulu et al. 2018).

Spatiotemporal expression patterns of five key genes in various regions of human brain

Additionally, to test if the key genes PPARγ, MAPK1, STAT3, RARA and APP causes the risk of AD, we searched the expression profiling of PPARγ, MAPK1, STAT3, RARA and APP in different regions human brain tissues utilizing the BRAINEAC data (Fig. 5). We identified that PPARγ, MAPK1, STAT3, RARA and APP are expressed differently in various brain regions, with the highest transcript level observed for MAPK1 in the putamen, followed by hippocampus, temporal cortex, frontal cortex, occipital cortex and thalamus. The least expression was observed in cerebral cortex for PPARγ, RARA and APP. Both RARA and PPARγ showed highest expression in the thalamus.

In order to evaluate the comparative temporospatial expression of PPARγ, MAPK1, STAT3, RARA, and APP in the human central nervous system (CNS), we searched the Human Brain Transcriptome (HBT) dataset (https://hbatlas.org/), a database based on Affymetrix GeneChip arrays (Keil et al. 2018). As is seen in Fig. 6, PPARγ, MAPK1, STAT3, RARA, and APP mRNA expression is consistent from conception to adulthood in all brain regions shown here which includes: the mediodorsal nucleus of the thalamus (MD), cerebellar cortex (CBC), amygdala region (AMY), striatum (STR), hippocampus (HIP) and neocortex (NCX). The highest expression was seen for APP followed by MAPK1 and STAT3. The temporal expression analysis showed that in
the case of RARA the expression level was high during fatal development, but the expression level gradually decreased as the human brain developed. The trajectory plot of PPARγ further tells that the expression of PPARγ mRNA expression is quite uniform from conception to adulthood in all depicted brain regions, including NCX, AMY, STR, MD, RARA and APP during fatal development (period 1–7), infancy (period 8–9), childhood (period 10–11), adolescence (period 12), and adulthood (period 13–15), in individual CNS areas.

### Table 3: Molecular Docking analysis results of Curcumin and shortlisted targets of protein showing Glide Score, energy of the docking and interacting amino acids

| Target Proteins | Glide energy (Kcal/mol) | Glide Score | Interacting Amino acids |
|-----------------|--------------------------|-------------|-------------------------|
| PPARγ           | -49.03                   | -7.269      | PHE 282, CYS 285, GLN 286, ARG 288, SER289, GLU 291, ALA 292, GLU 295, VAL 339, LEU 340, ILE 341, SER342, HIE 449, PHE 226, HIE 323, ILE 325, ILE 326, TYR 327, MET 329, LEU 330, LEU333 |
| MAPK1           | -43.637                  | -5.635      | VAL 37, ALA 33, ASP109, GLY32, GLU 31, ILE 29, MET 106, LEU105, ASP104, GLN 103, ALA 50, LYS 52, LEU154, ASN 152, LYS 149, ASP 147, ARG 65, THR188, LEU168, ASP 165, GLY 164, GLU 69 |
| STAT3           | -43.489                  | -5.329      | ILE 258, ASN257, PRO 256, GLY 253, CYS 251, ALA 250, GLN 247, SER 514, TRP 474, PRO 336, ASP 334, PRO 333, ARG 325, GLN 326, CYS 328 |
| RARA            | -34.122                  | -5.312      | TRP 225, PHE 228, SER 229, SER 232, PRO 407, PRO 408, LEU 409, ILE 410, GLN 411, VAL 395, ALA 392, ALA 389, SER 388, ARG 385, LYS 262, ALA 263, CYS 265, LEU 266, ASP 267, LEU 269, ARG 339 |
| APP             | -36.255                  | -3.980      | LYS 314, LEU 311, PHE 310, HIS 307, VAL 373, HIS 376, ALA 377, VAL 380, ILE 381, VAL 434, HIS 433, HIS 430, ARG 429, HIS 426 |
and CBC. All regions indicate a comparatively lower level of expression in early embryonal life which slowly increases during fetal development till birth and increase again postnatal life and early childhood up to adolescence (Fig. 6), which remains quite stable thereafter. It must be noted, however that PPARγ expression in the hippocampal region (blue line) behaves differently indicating a more significant rise in early postnatal life and persisting at higher levels (in comparison to other tissues) up to adulthood.

**Molecular docking of curcumin with key proteins**

Molecular docking studies helped us to better understand the binding interactions of the key proteins with the ligand molecule. The molecular docking of key proteins RARA, APP, PPARγ, STAT3, and MAPK1 with the curcumin was carried out using Glide. The glide score and glide binding energy for all the key genes are shown in Table 3. The results showed that a stronger interaction is present between the PPARγ molecule and curcumin having a Glide energy of 49.03 kcal/mol and a glide score of -7.269. The 2-D structure of the docking complex reveals that curcumin interacts with the amino acid GLU 295 in the active site (Fig. 7). The interacting amino acids of the various docking complex is given in (Table 3).

**Discussion**

Poor understanding of the mechanism and sudden emergence of the AD have made it difficult to identify the cause and prevent the progression of disease. The main mechanism of action of the drugs available in the market is to ease or prevent the amyloidogenic fragments. But the processing at the b-site by the b-secretase enzyme (BACE1) which results in the amyloidogenic and amyloidogenic fragments. But the processing of the Apolipoprotein A (APOE) which are major hallmarks in the AD (Zheng and Koo 2011; Kang and Müller-Hill 1990). These two genes are main targets for the treatment of AD. Another highly scored protein called Cathepsin D (CTSD) protein shows approximately 70% probability of causing AD. It is lysosomal protease which is responsible for the degradation of the amyloid plaques. It was reported that the levels of CTSD protein down regulated in the AD patients and is said to play a role in the deposition of the amyloid plaques in the cortex of the brain. Therefore, the levels of Cathepsin D may be used as a diagnostic biomarker for AD (Kim et al. 2021). Another Protein signalling called retinoic acid receptor (RAR)α signalling is reported to increase the expression of metalloprotease 10 and disintegrants that process the amyloid precursor protein and prevent its accumulation thereby preventing neuronal cell death associated with Aβ (Jarvis et al. 2010).

Enrichment analysis of the targets was also conducted using Enrichr and Metascape then the networks of the protein–protein interaction were carried out by Cytoscape 3.6. The target genes showed that they played an important role in GO biological processes that are mostly involved in regulation of inflammatory responses, regulation of protein phosphorylation and peptidyl-tyrosine modification. It is well established that due to disturbance in the balance of pro-inflammatory and anti-inflammatory signalling in the AD patients the chronic
inflammation occurs which further aggravates the pathogenesis (Kinney et al. 2018). Another hallmark for the AD is the neurofibrillary tangles (NFTs) which are formed due to hyperphosphorylation of the tau proteins at the multiple sites which results in the disintegration of the microtubule structure and disturbance of cellular processes (Guo et al. 2017; Kinney et al. 2018). Thus, regulation of these inflammatory signalling and protein phosphorylation is an important way to manage AD. Lipoxygenase (LOX), Cyclooxygenase (COX-2), and Inducible nitric oxide Synthase (iNOS) are important enzymes that regulate inflammatory processes. It is specified that curcumin possess anti-inflammatory action by hindering the Toll-like receptor 4-dependent, COX-2, LOX, iNOS and nuclear factor-kappaB signalling pathways and the activation of a peroxisome proliferator-activated receptor-gamma pathway (PPARγ) (Shimizu et al. 2019)(Menon and Sudheer 2007). Inflammation is also closely linked with the tumour formation therefore the curcumin shows chemo preventive role in the cancer formation (Menon and Sudheer 2007). PPARγ agonists have been reported to inhibit neuroinflammation and reducing amyloid and tau pathologies in few animal models and in the patients with mild AD but the molecular mechanism is not thoroughly investigated (Govindarajulu et al. 2018).

It was studied that the extracellular signal-regulated protein kinase (ERK MAPK)signalling is important for various forms of hippocampus-dependent memory and learning that are hindered in AD. Based on these studies it was further showed that inhibition of PPARγ prevents the recruitment of PPARγ to ERK which showed that formation of this protein complex is requisite for memory formation (Jahrling et al. 2014).

Synaptic plasticity changes are mainly reported as an important basic principle of cognitive processes such as memory formation, sensory processing, attention, associative learning, and decision making and retrieval, perception. Loss of synaptic plasticity or its dysregulation is considered major cause of Dementia or AD (Koopmans et al. 2019). The resources lack a comprehensive ontology of synaptic processes and locations so in order to overcome these shortcomings another tool called SynGO was used for ontology of synaptic genes. AD is distinguished by hippocampal-dependent dysfunction, cathepsins are also important for hippocampal-dependent learning and memory. It is reported that, cathepsins on being secreted in the extra cellular space produces extracellular effects on synaptic plasticity and neuroprotection thereby playing role in AD (Nie-meyer et al. 2020). The results of Enrichment analysis were also found compatible with the correlation between targets and phenotypes in VarElect Analysis.

PPI was constructed to understand the significance of curcumin targets. Applying network pharmacological approach to identify top five key genes namely, PPARγ, MAPK1, STAT3, KDR and APP. Further the expression profiling of these key genes in different human brain tissues was done utilizing the BRAINEAC data and comparative temporospatial expression human central nervous system (CNS), was done by exploring the Human Brain Transcriptome (HBT) dataset. At last, molecular docking was used to investigate the mechanism of interactions between curcumin and five key targets. The results indicated that PPARγ, MAPK1, STAT3, KDR and APP showed affinity with Curcumin. The results showed that the Curcumin has potential to bind with large active sites of PPARγ with good binding scores compared to all other proteins. Therefore, the precise mechanism of Curcumin on AD based on molecular docking need further validation using biological experiments.

Conclusion

This study provided a novel method to disclose the therapeutic mechanisms of Curcumin against AD. The results indicated that Curcumin may have an anti-AD effect through multiple targets, pathways, and biological processes. However, more future studies are required to confirm the precise mechanism and the clinical potential and mechanisms of curcumin against AD.

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Author contributions M.Z.M. conceived the model. D.A. M.A.I. and M.Z.M. prepared figures of the numerical results. D.A. M.A.I. M.M.U.H. S.D. and M.Z.M. analysed and interpreted the results. D.A. M.A.I., M.M.U.H., S.D., M.A.I. and M.Z.M wrote the manuscript. M.A.I and M.Z.M. supervised the study and approved the final draft.

Data availability The data used in the current study available from the corresponding author on reasonable request.

Declarations

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