In silico detection of dysregulated genes and molecular pathways in Alzheimer's disease as basis for food restoring approach

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Abstract

Forty-eight million people worldwide suffer from dementia, which is often associated with the growth of the elderly population. However, concerns are also arising as ~~regard~~ regards ~~of~~ the younger population, where acute and chronic abuse of alcohol and neurotoxic substances has been shown to cause permanent damage to the nervous system leading to some form of dementia. Sixty ~~per cent~~percent of dementia is Alzheimer's disease (AD). Most ~~of the applied~~ therapies used have been ~~resulted~~ unsuccessful. Genetic and epigenetic factors contribute to the pathogenesis of AD. Among the epigenetic mechanisms modulation of microRNA (miRs) plays an important role. In this study, we utilized bioinformatics tools to identify genes and pathways involved in Alzheimer's disease. A secondary analysis of previously published dysregulated miRNAs associated with Alzheimer's was conducted using Mienturnet, followed by pathway enrichment analysis with Reactome ~~To detect AD involved genes and pathways, a bioinformatic secondary analysis of published Alzheimer's dysregulated miRs was performed using Mienturnet followed by Reactome tools~~. Indeed, the data obtained from Mienturnet were ~~where~~ then used for Reactome interrogation. These platforms interrogation, allowed us to discover common putative genes (by Mienturnet) target of the dysregulated miRs and the pathways in which ~~theset~~ these altered genes are involved (by Reactome tool). The Beta-catenin phosphorylation cascade and Netrin-1 signaling, both downregulated in AD, emerged as the most significant. Lastly, based on the assumption that food bioactive compounds (BC) can modulate miRs, which in turn can modulate dysregulated genes and pathways associated with AD, a literature search, demonstrated that some BC are able to modulate the dysregulated pathways and genes. Indeed, curcumin, osthole, puerarin, xanthoceraside, sulforaphane, salvianolic acid A, resveratrol and andrographolide lead to upregulation of Wnt/Beta-catenin pathway. Choline, methionine, folate,

Comentado [T1]: What occurs with metabolic and vascular causes associated with oxidative stress and brain barrier?.

and vitamin B6/B12 modulate the upregulation of the Netrin-1 pathway. In conclusion, our *in silico* analysis of published miRs identified dysregulated genes and their associated pathways, thus advancing the knowledge of AD and providing important insights for diagnosis and therapy. In addition, we also indicated ~~the~~ that BC can~~able to~~ modulate the dysregulated miRs, their target ~~genes~~ gene expressions, and their associated pathways.

Introduction

The increase ~~of~~ in old-age population has led to the incidence of age-related diseases, including dementia, to a dramatic rise. Forty-eight million people worldwide suffer from dementia and its incidence doubles every 5 years from ages 65 to 90 years (https://www.alz.org/alzheimers-dementia/facts-figures). In addition, serious concerns are also arising as ~~regard~~ regards ~~of~~ the younger population, in which the acute and chronic abuse of alcohol and other neurotoxic substances revealed serious consequences and permanent damage to the nervous system leading to some form of dementia. Alzheimer's disease (AD) ~~account~~ accounts for 60-70% of dementia cases (Cummings et al., 2016). AD is considered one of the emergencies of the future: 47 million people in the world are suffering from AD. This figure is destined to rise to ~~the~~ a huge number of 131 million patients by 2050 (Prince et al., 2013).

To date it has not yet discovered an effective treatment for AD, only some therapies to alleviate the symptoms exist. Many resources ~~and many hopes~~ were invested in AD research, but they have failed, so ~~that~~ some of the most important world drug companies abandoned AD and ~~Parkinson~~ Parkinson's89 pharmacology research. Because of the lack of clear molecular mechanisms and the unsuccessful therapeutic approach, AD has become a major challenge in neurobiology of the 3rd millennium. In this apocalyptic framework, it is of paramount importance to explore other strategies of intervention based on and substantiated by a greater understanding of the molecular mechanisms underlying AD onset and progression also using the most updated resources such as the bioinformatic platforms, the high throughput analyses, and big data repositories.

The AD has a multifactorial etiopathogenesis. To AD pathogenesis concur both genetic factors, e.g. mutations of genes that regulate the metabolism of the Amyloid Precursor Protein (precursor of the β-amyloid peptide, the main component of the amyloid plaques), and environmental factors (Przedborski et al., 2003). The latter induce epigenetic modifications in our organism, leading to gene expression modification, without altering the nucleotide sequence. Epigenetics regards mechanisms that determine stable and heritable (but reversible) changes in the expression of genes without any alterations to the original DNA sequence. DNA methylation, histone modifications and miRs are the main epigenetic mechanisms involved in the pathophysiology of AD (Mastroeni et al., 2011; Paniri et al., 2023). MiRs represents a promising key for many diseases diagnosis and therapy, from cancer to neurodegenerative diseases, including AD (Femminella et al., 2015; Kaur et al., 2023). MiRs are small, non-coding, endogenous nucleotide sequences that negatively regulate the expression of their target genes in a post-transcriptional

Comentado [T2]: Please define AD, such as: formation of senile plaques by the accumulation of beta-amyloid proteins and Neurofibrillary Tangles….. hyperphosphorylation of tau protein….. …….and zones of brain affected. And two-hit hypothesis????

Comentado [T3]: The authors must include data, not opinions.

manner, inducing degradation or inhibition of target mRNA translation. Scientific evidence shows that some of these miRs are altered in patients with AD (Reddy et al., 2017).

MiRs functions have been investigated in this paper using bioinformatics approaches. Indeed, the advent of "systems ~~system~~ biology" and "Omics" technologies, the emergence of high-throughput data techniques and the existence of big data repositories, allow the interrogation of many cells features and determine the molecular network interacting with each other. It is thus possible to study biological systems through the acquisition of an extremely large number of molecular data and measurements~~,~~ and to understand and model the properties of the multiplicity of networks that control cell behavior. This approach can “view” the scheme and the rules that govern the system to anticipate how the other players, modulate~~connected to each other,~~ and ~~-~~are modified by the perturbation. It also represents a challenge for a branch of contemporary biology, ~~the~~ network biology, which represents a promising field ~~to understand~~for understanding cell structure and function. Furthermore, with the continuous improvement of computational and bioinformatic tools, now we can uncover the molecular mechanism responsible for the pathogenesis of different diseases, such as signaling pathways, biological processes, genes, miRs involved, and considered potential biomarkers. Many bioinformatics tools are now available to manage the flow of data. Most applications are accessible via an online interface. Mienturnet and Reactome tools were used in this work, and they allowed us to predict the putative target genes that the modulated miRs in AD interact with, and the pathways in which the same genes are involved. These tools can analyze a particular sequence located on the 5 'end of a miRs, called the seed region, ~~with the aim of predicting~~to predict the most probable genes that potentially interact with it.

Recent evidence suggests that some nutrients and food bioactive compounds ~~components~~ (BC), due to their ability to modify the expression/concentration of specific miRs, can protect the organism against certain diseases in which the alteration of their target genes is a fundamental part of the pathogenesis. Indeed, diet is an environmental factor that appears to be strongly related to AD through modification of epigenetic pathways (Athanasopoulos et al., 2016; Martínez-Iglesias et al., 2023). Assuming that altered miRs expression contributes to the development of AD, there is a possibility that “correcting” dysregulated miRs may be able to reverse the pathological process. Based on this assumption, nutrition plays an important role ~~through~~ in the modulation of miRs. Recent works showed the ability of natural bioactive compounds to regulate miRs expression (Vrânceanu et al., 2022). Bioactive compounds are a heterogeneous group of substances commonly introduced with daily diet, able to positively influence health, contributing to the prevention of different diseases, even if they cannot be considered nutrients in the strict sense. In plants, they represent the secondary metabolites, where they play a function of defense against free radicals, viruses, bacteria, and fungi. They are widely distributed in fruit, vegetables, legumes, whole grains, nuts, seeds, mushrooms, herbs, ~~and~~ spices and ~~in~~ plant-based beverages such as wine and tea (Barbieri et al., 2017). The analysis of the properties of bioactive compounds opened the broad field of "functional food”. Through an original bioinformatic analysis (*in silico*) of the available data, this article aims to 1) discover dysregulated genes and molecular pathways in AD and 2) map natural and food-related compounds that ~~have the ability to~~can modulate the expression of altered miRs associated with

AD and their dysregulated pathways and gene ~~with the aim of discovering~~to discover bioactive molecules that could delay or halt the progression of the disease.

Materials & Methods

~~Literature~~ A literature search was performed using the PubMed free online database for the collection of ~~AD dysregulated~~AD-dysregulated miRs. Scientific papers with experimental evidence of modulation of miRs in AD (up/down regulated) have been collected using the following keywords: "microRNA and neurodegenerative disease" or “microRNA and ~~Alzheimer~~ Alzheimer's disease”. The search resulted in a list of 1537 papers, from which a total of 47 papers been considered. Only articles published in English were included in this review. The types of studies considered for inclusion were those involving ~~human~~humans both~~Human~~ *in vivo* or clinical and *in vitro* studies from 2008 to recently were considered, to be sure about the relevance and currency of the information.~~.~~ *In vitro* studies regarded solid tissues, biological fluids, and cell culture, all from human origin. In addition, the studies included in the work were those directly involved in the modulation of miRs. Studies that used animal or cellular models not relevant to the research context, such as those involving species or tissues not comparable to humans, were also excluded.

The same approach was used to search for BC capable of modulating both miRs found altered in AD or related pathways and genes of interest. The specific keyword has been used like “bioactive compounds and microRNAs” or “natural compounds and microRNA” or natural compounds and the pathways found in our bioinformatic interrogations as specified in the results, “Netrin-1 and natural compounds” or “food bioactive compounds and Wnt/Beta-catenin pathway”. Initially, a broad search was conducted across multiple databases (Pubmed, Google Scholar). The inclusion criteria focused on studies related to brain cells or models specifically linked to Alzheimer’s disease. Both cellular models and animal or human models were considered, aiming to explore the processes and mechanisms involved in the development and progression of the disease within the central nervous system. We, thus, collected published data focusing on the detection of BC which ~~show~~shows therapeutic value to promote the restoration of dysregulated pathways or miRs. After retrieving the initial pool of studies, duplicates were removed, and a screening of titles and abstracts was performed to exclude irrelevant articles. Full-text articles were then reviewed to assess their eligibility based on this specific inclusion criteria, such as the study’s relevance to bioactive compounds, miRNA interactions, and interaction with ~~ours~~our interested pathways. Only studies written in English were considered and those that did not meet these criteria were excluded.

Bioinformatics analysis

Bioinformatic analysis was conducted using Mienturnet and Reactome tools. To analyze the interactions between genes and miRs involved in the etiology of AD, the microRNA ENrichment TURned NETwork (MIENTURNET) was used (Licursi et al., 2019). This tool is an easy-to-use web tool that receives an input list of miRs and uses “miRNA-target interactions”

computationally predicted and experimentally validated downloaded from TargetScan and miRTarBase, respectively.

By entering into Minturnet an input list containing the ID of each miRs, obtained from miRBase (a database of miRs sequences and annotations), the program takes into consideration both computational and experimental evidence. Mienturnet, thus, allows to visualize the resulting genes (with their statistical significance) as miR-target network interactions. ~~interaction~~ The program processes the input file and provides in the 'IDs found' drop-down menu the total number of miRs recognized from the miRBase database along with a table that includes: the name of the miRs, the accession ID in miRBase of the microRNA, as well as hyperlinks to miRBase and the sequence of the mature miRs. Unknown miRs can be found by clicking on the 'IDs not found' drop-down menu. By clicking the miRNA-target Enrichment box, Mienturnet performs a statistical analysis for over-representation of miRNA-target interactions included in the list of input miRs. On the miR-target Enrichment page, it is possible to select the database to which you want to refer to for the enrichment analysis of microRNA-target interactions (TargetScan and/or miRTarBase). We referred to TargetScan, that appeared as the most up-to-date tool for sequence-based miRNA-target predictions. By checking the TargetScan box, computationally predicted miRNA-target interactions are considered. TargetScan predicts the biological targets of miRs by searching for conserved sites, that allow matching with the “seed region” of each miRNA (Agarwal et al., 2015; McGeary et al., 2019).

Subsequently, we used Reactome platform to identify the pathways of related genes. Reactome is a free, open-source, open-data, curated and peer-reviewed pathways database, that includes bioinformatic tools for the visualization, interpretation and analysis of pathways to support basic research (Gillespie et al., 2022). The central component of Reactome is the pathway, as it visually represents how nucleic acids, proteins, complexes and other small molecules are involved in biological pathways (apoptosis, energy metabolism, innate and adaptative immune response etc.). For our study we used “Analysis Tools”, a feature available on the Reactome web interface. Different types of analysis can be conducted based on the format of the input data; we used gene nomenclatures, inserting list of genes resulting from the analysis we carried out by Mienturnet. Reactome identifies for each input list of genes entered, the pathways in which the genes are involved, and selects, based on the p-value, the top 25 most significant pathways (Pathways Analysis Report). In figure 1 we summarized the sequence of our bioinformatic experimental procedure.

After the detection of statistically significant genes and pathways resulting from our bioinformatic analysis through Mienturnet and Reactome, we searched in the published data, for natural BC able to modulate AD dysregulated pathways, genes and miRs involved. Using the STITCH database (Search Tool for Interactions of Chemicals), we found intermediate molecules that interacted with the most important target genes that we had previously found through Mienturnet analysis. STITCH collects and integrates data from different sources to explore and predict interactions between compounds and proteins. It uses experiments, databases and literature to find chemicals that are associated with other chemicals and proteins. In the present

study, the genes of interest found through our interrogation were entered into the STITCH database and human species were set up to screen the target proteins that interact with them (Szklarczyk et al., 2016).

Results

Based on our proposed secondary analysis of previously published datasets, this work aims to answer biologically and medically relevant questions in AD different from those ~~that~~ of the original works. Indeed, we interrogated bioinformatic tools to discover genes target and pathways of miRs selectively up-regulated and down-regulated in AD. The input data we entered, were the pool of experimental and clinical published data on Alzheimer's disease, in which the levels of miRs were assessed in human samples and cellular models (Table S1). MiRs that were up and downregulated in AD, are analyzed by Mienturnet platform. To conduct the analysis, TargetScan platform was chosen as the reference database for microRNA-target interactions. For downregulated miRs, out of the 140 miRs inserted, 77 were recognized by the program and analyzed. The remaining 66 miRs were not recognized and reported in the "IDs not found" panel, because they are not present in the databases used by Mienturnet, thus evidencing a lack in the database. For upregulated miRs, 152 were recognized and analyzed out of 155 miRs inserted. The input lists used for the analysis in Mienturnet are provided in Supplemental Data as Table S2 (input-list miRs DOWN) and Table S3 (input-list miRs UP).

~~Results w~~We obtained the results by Mienturnet analysis are reported in Table S4 (target genes of downregulated miRs and their p-value) and Table S5 (target genes of upregulated miRs and their p-value). These files show target genes for each miRs from the input list. For each gene, the number of interactions and the miRs that interact with them are also indicated. Table 1 and Table 2 show the most significant altered genes from the Mienturnet analysis (selected by their p-value). We used the results for further analysis using the open-source tool Reactome.

The results obtained from the Reactome analysis are reported in Article S1 (Report Genes microRNA-Down) and Article S2 (Report Genes microRNA-Up). The results yielded the Beta-catenin phosphorylation cascade pathway (Pathway Analysis Report-genes microRNA-Down) and Netrin-1 signaling (Pathway Analysis Report-genes microRNA-Up) as the most significant ones (p-value 0,003). Our analysis showed that FRAT2 and PPP2R5E, which are target genes of downregulated miRs in AD, are involved in the Beta-catenin phosphorylation cascade pathway.

As a result of the enrichment analysis we performed by Mienturnet, we evidenced that FRAT2 is found to be a target gene of the following miRs: has-miR-221-3p, has-miR-22-3p, has-miR-23a-3p, has-23b-3p, has-miR-26a-5p, miR-26b-5p, has-miR-29b-3p; while PPP2R5E is found to be targeted by miR-132-3p, has-miR-212-3p, has-miR-133b, has-miR-148a-3p, has-miR-181c-5p, has-miR-200a-3p, has-miR-221-3p, has-miR-23a-3p, has-miR-23b-3p, has-miR-301a-3p, has-miR-342-3p and has-miR502-3p.

In the pathway mediated by Netrin-1 signaling, the NEO1 gene is involved. From the enrichment analysis we performed by Mienturnet, NEO1 is a target gene of following up-regulated miRs in AD: has-miR-125a-5p, has-miR-125b-5p, has-miR-128-3p, has-miR-128-5p, has-miR-216a-3p,

has-miR-216a-5p, has-miR-216b-5p, has-miR-27b-3p, has-miR-374a-5p, has-miR-429, has-miR-92a-3p, has-miR-92b-3p, has-miR-9-5p.

~~By means of~~Using Reactome analysis we identified additional pathways associated with down-regulated miRs, including SUMOylation of DNA damage response and repair proteins (involving the POM121C and STAG1 genes) and Regulation of PTEN mRNA translation (involving the PTEN gene), with p-values of 0.006 and 0.007, respectively. For upregulated miRs, the pathways identified were Editosome Formation (involving the A1CF gene) and mRNA Editing: C to U conversion (also involving the A1CF gene), with p-values of 0.01 and 0.013, respectively (see Article S1 and S2 in Supplemental Data).

Bioactive Compounds

To give a clinical meaning to our above reported original results, we searched in the published literature on the matter, for natural BC able to modulate both pathways (i.e. Wnt-β-catenin and Netrin-1), and miRs differentially expressed in AD. No data on gene expression regulation by BC was found.

~~We, thus, collected published data focusing on issues other than ours, the latter focusing on the detection of BC which show therapeutic value to promote the restoration of dysregulated pathways.~~ This search has allowed us the ~~identification~~ identify ~~of~~ BC and food components that have demonstrated the ability ~~of acting~~to act on intermediates, namely:~~such as~~ Glycogen synthase kinase-3 beta (Gsk3ß), ~~β-amyloid precursor protein (APP),~~ Dishevellesproteins (Dvl) or Netrin receptor DCC (DCC), based on our interrogation through STITCH tool, molecules that interact with FRAT2 gene (Gsk3ß, Dvl) and NEO1 gene (Dcc) (Figure 2,3). Although not identified as intermediary molecules in the STITCH search, we also considered BC due to its impact on the β-amyloid precursor protein (APP), a critical component in Alzheimer's disease pathology. This consideration enhances our understanding of the disease's pathogenic mechanisms. ~~Although not found as intermediary molecules in the STITCH search, we also considered BC that affect the β-amyloid precursor protein (APP), which is essential for its key role in AD, thus contributing significantly to the understanding of the disease's pathogenic mechanisms.~~

~~and~~ Figure 4 and Figure 5~~3~~, report ~~a schematic representations~~schematic representations of food BC and nutrients, found to be able to restore our pathways of interest. Curcumin, osthole, puerarin, resveratrol, ginkgolide B, salvianolic acid A, andrographolide, xanthoceraside, and sulforaphane are involved in the neuroprotective role through activation of Wnt-β-catenin pathway, downregulated in AD. On the other hand, some nutrients such as ~~coline~~choline, methionine, B6/B12 vitamins, and folate explain their potential neuroprotective effect by maintaining the level of Netrin-1.

Discussion

Alzheimer's disease~~Alzheimer~~ is a devastating disease and the most common cause of dementia in the world~~worldwide~~ and it is increasing dramatically ~~increasing~~. There is no ~~actually~~ actual curative treatment, therefore a tremendous need exists for discovering novel therapeutic approaches. ~~At~~ In this regard, to make a meaningful contribution to the literature and increase the

knowledge ~~on~~ of AD, we performed a secondary analysis by applying appropriate open-source computational tools interrogations. This allowed us to identify~~,~~ the target genes of dysregulated miRs and ultimately the pathways in which these genes are involved. We also successfully obtained insights into food BC and their impact on these modified pathways. The rationale for such an approach is represented by the observation that some miRs may be modulated by food BC (Vrânceanu et al., 2022). This modulation might in turn modulate dysregulated genes responsible for~~of~~ AD, aiming to restore their expression to a healthy phenotype. Indeed, recent studies have shown that dysregulation of specific miRs plays a critical role in the development of AD (Reddy et al., 2017).

This has prompted researchers to develop therapeutic strategies based on these miRs, because available therapies have not been successful in treating or slowing the progression of AD. The therapeutic modulation of miRs can be achieved in two ways (Angelucci et.al 2019; Theron et.al 2023): 1) inhibiting the function of miRs through a single-stranded antisense oligonucleotide (ASO) complementary to the miRs; 2) increasing or restoring physiological levels of miRs through the administration of compounds that stimulate their production or through a double-stranded synthetic miR that mimics the function of endogenous miRs.

Defining interventions based on miRs, that simultaneously restore various altered pathways in AD, represents up to now one of the most promising prospects for AD treatment. The increasing evidence emphasizing the importance of miRs dysregulation in AD has led us to investigate, the biological function of miRs to identify altered pathways associated with them.

Our *in silico* analysis has allowed to obtained information regarding miRs of interest, identifying their target genes and the pathways in which these genes are involved. The results showed that Beta-catenin phosphorylation cascade and Netrin-1 signaling, are the most significant pathways. Previous observations (Ju et al., 2022; Ramakrishna et al., 2023) ~~which~~ found decreased Netrin-1 in AD (Ju et al., 2022) and WNT-β Catenin as a possible target for neurodegenerative diseases therapeutic intervention (Ramakrishna et al., 2023). Through bioinformatic research, we identified these pathways in association with down-regulated miRs. Our hypothesis, is that this discrepancy could be explained by additional regulatory mechanisms, or the interplay of other microRNAs targeting the same gene, which could inhibit the pathway despite the downregulation of the miRs that normally target it. Factors such as oxidative stress, neuroinflammation or epigenetic changes, all common in AD pathology, could contribute to the overall downregulation of beta-catenin signaling, overriding the expected effects of miRNA downregulation. In addition, recent results show that in some cases microRNAs can also upregulate gene expression (Orang et al., 2014). This may further complicate the picture of the molecular networks involved in cell signaling and highlights the need for studies such as ours.

In the central nervous system (SNC) the Wnt/B-catenin pathway is essential in signal transduction, regulating numerous cellular processes like neuronal survival, neurogenesis, regulation of synaptic plasticity and integrity of the blood-brain barrier (Aghaizu et al., 2020). Some evidence of the involvement of Wnt signaling pathway in AD, has been proposed (Jia et al., 2019), and down-regulation of Wnt signaling contributes to the pathogenesis of AD (Ramakrishna et al., 2023). Caricasole et al., 2004 and Rosi et al., 2010 show that the canonical

Wnt antagonist Dickkopf-1 (Dkk1) is up regulated in brain of AD patients and mouse models. Dkk1 inhibits canonical Wnt signaling by interacting with LRP5/6 Wnt co-receptors, thus impairing the binding of Wnt proteins to both Frizzled and LRP5/6. The inhibition of Wnt signaling by Dkk1 leads to increased Gsk3ß activity and reduced cytoplasmic β -catenin levels both features which are observed in the brains of AD patients. The increase in Gsk3ß kinase activity, observed in the AD brain, contributes to the hyperphosphorylation of Tau protein, distinctive pathological trait of the disease (Salcedo-Tello et al., 2011). Overexpression of Gsk3ß in the brain leads to neurodegeneration and learning deficit. The increased activity of Gsk3ß promotes degradation of β-catenin, leading to a reduction in the canonical pathway (Mateo et al., 2006).

Netrin-1 is an endogenous secreted laminin-related protein identified as a bifunctional neuronal guidance molecule, through its interactions with canonical receptors. It influences axonal growth and plays a key role in axon arborization, dendritic growth and synapse formation interacting with its receptors such as deleted in DCC and Uncordinated-5 (UNC5) (Xia et al., 2022). Netrin-1 acts as a negative regulator of Aβ production through its interaction with the APP, from which Aβ, the main component of the amyloid plaques associated with Alzheimer, is derived (Lourenço et al., 2009). The reduction in Netrin-1 production in the brain of transgenic mice (considered as AD model), was associated with the increase in Aβ concentration. Aβ-induced neurotoxicity has been accepted as a hallmark component in the pathogenesis of AD (Borel et al., 2017; Rama et al., 2012). Decrease in Netrin-1 was also correlated to a Th17/Tregs (T helper 17/regulatory T cells) balance disorder in a rat model of Aβ-induced AD (Sun et al., 2019). Th17 cells are proinflammatory, while Tregs play an essential role in maintaining immunological homeostasis and regulating autoimmunity. In serum and cerebrospinal fluid of AD mouse model, the reduced level of Netrin-1 appears to be related with an increase in Th17 cells and reduction of Tregs. This imbalance leads to inflammatory process, a key component in AD pathogenesis (Kiraly et al., 2023).

Other pathways related to Alzheimer's pathogenesis were identified but not considered due to a less significant p-value. For down-regulated miRs were found SUMOylation of DNA damage response and repair proteins and Regulation of PTEN mRNA translation.

SUMOylation is a post-translational modification that involves attaching SUMO proteins to lysine residues in proteins, regulating processes such as DNA repair, transcription, and stress response. In the context of neurodegenerative diseases, dysregulation of SUMOylation is linked to AD pathogenesis (Mandel & Agarwal, 2022). Studies in transgenic mouse models, have shown changes in SUMO protein expression, particularly SUMO1, in cortical and hippocampal tissues, which are associated with learning and memory deficits (Krumova et al., 2011).

SUMOylation appears to modulate the formation of amyloid-beta (Aβ) plaques by modifying APP (Zhang & Sarge, 2008).

Regarding the pathway Regulation of PTEN mRNA translation, different studies evidence involvement of PTEN deregulation in neurodegenerative disease and AD (Ferrarelli, 2016). The study of Griffin et al., 2005 suggested that in AD there is an activation of the Akt/PKB pathway with increased phosphorylation of Akt substrates. At the same time, PTEN (a tumour suppressor

and negative regulator of Akt) undergoes loss of function or altered distribution. This PTEN dysfunction leads to over-activation of the Akt pathway, which disrupts normal cellular processes such as neuronal survival, autophagy and protein degradation. These changes contribute to the accumulation of toxic proteins such as amyloid-beta and tau, which play an important role in the progression of AD pathology.

The pathways found with Reactome connected to miRs up-regulated were: Formation of editosome and mRNA editing: C to U conversion.

Editosome is a protein complex responsible for RNA editing, which alters RNA sequences after transcription. RNA editing, the process that alters individual bases of RNA, may contribute to AD pathogenesis due to its roles in neuronal development and immune regulation and could represent an important post-transcriptional regulatory program in AD pathogenesis.

Regarding the pathway, mRNA editing: C to U conversion, this is a specific type of RNA editing where a cytosine (C) is converted to uridine (U) in mRNA. The most common type of RNA editing is the deamination of adenosine (A) bases to inosine (I) by the Adenosine Deaminase RNA Specific (ADAR) family of enzymes, and the second is the deamination of cytidine (C) to uridine (U) by the activation induced cytidine deaminase (AID)/apolipoprotein B editing complex (APOBEC, is an enzyme in mammals that plays a specific role in RNA editing) cytidine deaminases (Polson et al., 1991;Bass, 2002). This modification can change the encoded protein. In AD abnormalities in this type of RNA editing may result in defective proteins involved in neuron protection, inflammation, or protein aggregation (like amyloid-beta or tau). These faulty proteins could contribute to the progression of the disease, including memory loss and cognitive decline.

The A1CF gene-target of up-regulated miRs, is found in both pathways. If the A1CF gene, which encodes the APOBEC1 is downregulated, this can have significant consequences for the formation of the editosome and the C-to-U RNA editing process. When A1CF is downregulated, the APOBEC1 enzyme may not be able to perform its C-to-U editing efficiently or accurately, leading to a reduction or loss of RNA editing at certain target sites. RNA editing, specifically C-to-U conversion, modifies protein sequences by changing the codons in mRNA. If this editing is disrupted due to a lack of A1CF, some proteins that depend on these changes after transcription may be produced in their original, non-functional forms. As a result, these proteins may become defective and unable to carry out their normal roles in the cell. In neurons, this could affect proteins that are essential for key processes such as communication between synapses, handling cellular stress, or degrading other proteins. All these process and consequences, potentially contributing to the progression of Alzheimer's disease by impairing neuronal function and increasing cellular stress and degeneration (Karagianni et al., 2022; Lerner et al., 2018).

Building on scientific evidence highlighting the use of natural products in the treatment of various pathologies and recognizing the role of nutrition in maintaining good health, we attempted to propose an approach for modulating these altered pathways (i.e. Wnt/β-catenin and Netrin-1) in AD. Through a search on PubMed, we found that many BC have been identified as potential modulators of the Wnt/ β-catenin signaling pathway and Netrin-1 as reported in the results. Some of these BC (such as curcumin, resveratrol and sulforaphane) may be direct

assumed through regular daily diet, from plant used for nutritional purpose (*Curcuma longa* (turmeric), *Brassicaceae* (broccoli and cabbage) and *Vitis vinifera* (wine,grapes). On the other hand, medicinal plants such as *Cnidium monnieri, Pueraria lobata , Xanthoceras sorbifolium, Salvia miltiorrhiza* (danshen) and *Andrographis paniculata* are used primarily to treat specific medical conditions. Their compounds, such as osthole, puerarin, xanthoceraside, salvianolic acid and andrographolide, have pharmacological properties that make them effective in therapeutic contexts rather than nutritional ones. This distinction is crucial because bioactives from medicinal plants are often associated with controlled use, unlike compounds found in nutritional plants, which are safe for regular consumption.

Below, we discuss some molecular insight related to the BC found to be effective on AD.

Curcumin, a polyphenol from the rhizome of *Curcuma Longa* L., a flowering plant from *Zingiberaceae* family, induces neurogenesis by modulation of Wnt/ β-catenin signaling pathway. Tiwari et al., 2016 developed nanoparticles encapsulating curcumin and demonstrated that these nanoparticles can induce hippocampal neurogenesis, neuronal proliferation, and differentiation in an Aβ-induced AD model in rats, through activation of Wnt/β-catenin pathway. *C. longa* extract significantly reduces the expression of Gsk3ß mRNA and protein in a dose-and time-dependent manner, in an *in vitro* study (X. Zhang et al., 2011). Curcumin increases β-catenin mRNA and protein, as well as the transcription factor Cyclin D1, in a dose-dependent manner, activating the Wnt-pathway.

Curcumin clinical trials showed controversial results. Thota et al., 2020, demonstrated that curcumin supplementation significantly reduced circulating GSK-3β. Conversely, Baum et al., 2008, evidenced no significant differences in Mini-Mental State Examination scores or plasma Aβ40 levels over 6 months of observation, and no adverse effects in AD patients, also. However, the authors emphasised the importance of further studies with longer periods of observation and, conversely, with additional endpoints.

Osthole~~Osthol~~ is derived from coumarin found in different herbaceous plants such as *Cnidium monnieri* (L.) Cusson ex Juss and *Angelica pubescens* Maxim.~~,~~ widely used in traditional Chinese medicine. Yao et al., 2015 suggested that osthole~~osthol~~ treatment (100 μmol/L) enhances the APP-overexpressing neural stem cells (APP-NSCs) proliferation, their differentiation into neurons and β-catenin mRNA expression, while it decreases the apoptosis and the accumulation of Aβ-42 and Gsk3ß activity. By activating the Wnt-β catenin pathway, it increases the proliferation of neural stem cells, neuronal differentiation and inhibits neuronal apoptosis. Potentially, it plays a role in prevention and treatment of AD (Singh & Bhatti, 2023).

Puerarin is an isoflavone compound derived from *Pueraria lobata* (Willd.) Ohwi used in traditional Chinese medicine. Accumulating evidence has indicated that puerarin has multiple pharmacological effects and exhibits potential treatment for various neurological diseases (X. Liu et al., 2023). Yao et al., 2017 demonstrated that puerarin attenuates the hyperphosphorylation of tau protein induced by Aβ1-42 in SH-SY5Y human cells through the inhibition of Gsk3ß expression, induction of β-catenin and cyclin D1 expression and subsequent activation of the Wnt/β-catenin pathway.

Xanthoceraside is another herbal molecule (triterpenoid saponin) extracted from the pericarp of *Xanthoceras sorbifolium* Bunge. In the hippocampus of APP/PS1 mice, the positive effect of xanthoceraside could be attributed to the increase of Wnt3a expression, the enhanced translocation of β-catenin to the nucleus and the increase ~~the~~ levels of inactive Gsk3ß. It can also promote the proliferation and differentiation of neural stem cells into neurons, thus improving learning and memory impairment in transgenic mice (Zhu et al., 2018).

Sulforaphane is a phytocompound belonging to the isothiocyanate family. It is present in sprouts of many cruciferous vegetables like cabbage, broccoli, cauliflower, and brussels sprouts. Sulforaphane is produced by the conversion of glucoraphanin through the enzyme myrosinase, which leads to the formation of this isothiocyanate. It is characterized by antioxidant, anti-inflammatory and anti-apoptotic properties (Panjwani et al., 2018). Several studies have demonstrated the effects of sulforaphane against neurodegeneration (Alfieri et al., 2013; Ping et al., 2010). Han et al., 2017, have highlighted how this molecule leads to up-regulation of Wnt pathway proteins, including β-catenin and cyclin D, promoting proliferation and differentiation of neural stem cells into neurons (Han et al., 2017; Schepici et al., 2020).

Andrographolide is a labdane diterpenoid extracts from the leaves of *Andrographis paniculata* (Burm.f.) Wall ex Nees a plant traditionally used in China and India as a natural remedy for inflammatory process. Tapia-Rojas et al., 2015, showed that andrographolide is a potent activator of Wnt signaling by inducing the transcription of Wnt targets genes, inhibiting Gsk3ß and increasing the level of β-catenin expression.

Salvianolic acid A is one of most important polyphenolic components extracted from the roots of *Salvia miltiorrhiza* Bunge (also known as Danshen), a traditional Chinese herb. Studies have shown that Salvianolic acid A can have a neuroprotective effect (Ling et al., 2021; Song et al., 2019). Animal studies highlighted how the administration of Salvianolic acid A significantly enhanced the proliferation, migration and differentiation of neural stem/progenitor cells (NPCs) into neurons. The induced neurogenesis was correlated with the activation of the Wnt3a/Gsk3ß/β-catenin signaling pathways and downstream target genes (Chien et al., 2016; S. Zhang et al., 2022).

Resveratrol is a naturally available polyphenolic compound with antioxidant, anti-cancerous, anti-inflammatory, and anti-aging properties (Albuquerque et al., 2015; Gambini et al., 2015). It is a polyphenol plant secondary metabolite commonly found in grapevines, grape juice, and wine. Surprisingly, also peanuts, pomegranate, spinach and banana contain high concentrations of resveratrol (Quadros Gomes et al., 2018). Surya et al., 2023 present new findings regarding how resveratrol regulates hippocampal neurogenesis through the Wnt signaling pathway, offering potential implications for neurotherapy. They propose that resveratrol could modulate Wnt signaling in several ways, potentially by elevating Sirtuin 1 (SIRT1) levels. This elevated SIRT1 activity, may act in Dvl to prevent the degradation of β-catenin from proteasomal degradation independently of the Wnt ligand (Holloway et al., 2010). Additionally, through deacetylation, SIRT1 could facilitate the movement of β-catenin into the cell nucleus, thereby promoting the transcription of Wnt target genes, independently of the ligand. Palomera-Avalos et al., 2017 demonstrated how resveratrol inhibits the activity of Gsk3ß, inducing changes in the expression

of axin1 and Dvl3, increasing β-catenin levels, thereby restoring Wnt/β-catenin pathway and thus exerting a neuroprotective role in mouse models (SAMP8- Senescence-accelerated prone mice P8). It has been noted that the administration of resveratrol in clinical trials for patients with AD and stroke yielded positive outcomes (Berman et al., 2017).

One of the first clinical studies mild to moderate AD evaluating the effects of resveratrol was conducted by Turner et al., 2015. This randomized, double-blinded, placebo-controlled phase II study revealed that resveratrol had safety and good tolerance among patients. Notably, the compound was detectable in the cerebrospinal fluid (CSF), indicating its ability to penetrate the blood-brain barrier, even if the study did not find conclusive evidence of neuroprotective benefits. However, the same research group analyzed sample of CSF and plasma from a subset of AD patients with CSF Aβ42 concentrations < 600 ng/mL. Resveratrol exhibited a reduction in the levels of metalloproteinase (MMP). This result suggested an increased maintenance of integrity of the blood-brain barrier and reduced infiltration of immune cells. Moreover, resveratrol exhibited regulatory effects on neuroinflammation, induced adaptative immunity and mitigated the progression of cognitive decline (Moussa et al., 2017).

Ginkgolide B, a terpenoid extracted from the *Ginkgo biloba* L. can enhance the presence of β-catenin in the cell nucleus, probably by inhibiting Gsk3ß. It activates the Wnt/β-catenin pathway, thus promoting the differentiation of neural stem cells (C. Li et al., 2022; M. Y. Li et al., 2018).

The extract derived from *G. biloba* L. comprises components like ginkgolides, bilobalide, quercetin and isorhamnetin. These constituents have demonstrated a significant influence on neural cell proliferation, as evidenced by findings from both clinical trials and animal (Ihl et al., 2012; Nada et al., 2014). The results from study conducted by Mazza et al., 2006 confirmed the clinical efficacy of *G. biloba* in the dementia of the Alzheimer type, comparable with donepezil clinical efficacy. Conversely, the study conducted by DeKosky et al., 2008 demonstrated that *G. biloba* at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with Mild Cognitive Impairments (MCI).

All these mentioned natural compounds have the ability to up-regulate the down-regulated Wnt/β-catenin pathway in AD. They act on the Gsk3ß kinase, responsible for the phosphorylation of β-catenin, redirecting it towards proteasomal degradation. This promotes an increase in the amount of non-phosphorylated active β-catenin, essential for the proper functioning of the signaling pathway and playing a neuroprotective role.

Regarding Netrin-1 pathway, among the dietary components that allow its modulation, upregulating it, we identified some BC reported in the results and below discussed.

Choline is an essential nutrient needed for the structural integrity and signaling functions of cell membranes, for acetylcholine synthesis (a crucial neurotransmitter for the brain and central nervous system functions, including memory and muscle control) and for methyl group metabolism (Gong et al., 2023). It's an amine that can be synthesized de novo by methylation of phosphatidylethanolamine. Despite *de novo* synthesis, it's insufficient to fulfill all biological functions. Choline is present in human milk, egg yolks, soy seeds, wheat germ, meat and brewer's yeast (Zeisel & Da Costa, 2009).

Albright et al., 2005 observed that the availability of maternal dietary choline, during mice gestation, can influence the levels of Netrin-1 and DCC. This intake contributes to the modulation of neurogenesis, neuronal migration, cell survival and differentiation during fetal development. Inadequate choline intake during gestation, may lead to neuronal defects at birth and impairment of cognitive postnatal abilities (Y. Wang et al., 2016). Choline supplementation, as demonstrated by several studies conducted on mice, reduces and prevents normal age-related cognitive decline (Velazquez et al., 2020).

Another compound important for the Netrin1 pathway, is the essential amino acid methionine. It is present in high levels in nuts, beef, lamb, turkey, fish, shellfish, cheese, eggs, dairy products and beans.

Other essential components are vitamin B6 and B12 and folate which exert their potential neuroprotective effect by maintaining the level of Netrin-1.

Folates and vitamins B6 and B12 are essential for homocysteine metabolism, which occurs via remethylation of methionine or transsulfuration to cysteine. In different study, it was observed that diets that are high in methionine, low in folate and deficient in vitamin B6/B12 have been associated with various issues such as vascular leakage, cerebral vascular dysfunction, short-term memory loss and neurodegeneration (Nuru et al., 2018; Weekman et al., 2019). Mice fed with a diet high in methionine, low in folate and vitamins exhibited a reduction in the expression of the Netrin-1 protein and an increase in the methylation of the Netrin-1 gene promoter, as determined through methylation-sensitive restriction enzyme-polymerase chain reaction analysis (Kalani et al., 2019). The link between Netrin-1 and memory was established by administering netrin, which significantly restored long-term fear-motivated memory. Data suggests that the reduction in Netrin-1 expression resulting from the hypermethylation of its gene could be linked to memory loss (Nuru et al., 2018). As report in the results, we identified those altered miRs that target genes involved in the two identified pathways of interest (Wnt-Beta catenin phosphorylation and Netrin-1). These miRs themselves could be modulated by BC. Pogue et al., 2011 revealed that curcumin effectively decreased the levels of miR-146 and miR-125b. In primary neurons, elevated expression of miR-125b leads to Tau phosphorylation and an increase in p53, cdk5 and p44/42-MAPK signaling (Banzhaf-Strathmann et al., 2014). Moreover, the increased expression of miR-125b led to a notable elevation in the levels of APP and β-secretase 1 (BACE1), contributing to the production of Aβ peptide (Jin et al., 2018). From the enrichment analysis we conducted by Mienturnet, miR-125b-3p was found upregulated in AD, targeting the Neogenin-1 (NEO1) gene, which is involved in the Netrin-1 pathway. NEO1 is a versatile transmembrane receptor that is involved in axonal guidance, neuronal differentiation, morphogenesis and cell death (Wilson & Key, 2007). Curcumin-induced downregulation of miR-125b could potentially influence the expression of NEO1 and Netrin-1 with an impact on pathways associated with axon growth and neural guidance. However, it's crucial to consider that molecular biology is complex, and effects can vary based on numerous factors.

MiR-132-3p found downregulated in AD, is often referred to as "NeurimmiR" due to its involvement in various neurophysiological and pathological processes. Emerging preclinical findings suggest that miR-132 may play a role in the progression of Aβ and tau pathology.

Comentado [T4]: Please include the bioinformatic analysis and MAPK pathways of Jara-Medina K, Lillo L, Lagunas C, Cabello-Guzmán G, Valenzuela-Melgarejo FJ. Identification of Vascular Genes Differentially Expressed in the Brain of Patients with Alzheimer's Disease. Curr Vasc Pharmacol. 2024;22(6):404-416. doi: 10.2174/0115701611298073240612050741. PMID: 38910465.

Additionally, clinical studies have suggested that reduced circulating levels of miR-132 could act as a potential diagnostic biomarker in AD (Lau et al., 2013; Pichler et al., 2017; M. Zhang & Bian, 2021). The study of Ge et al., 2020 highlighted how berberine treatment could attenuate the neuronal damage in neuronal cells induced by Aβ-25-35, through up-regulation of miR-132-3p expression. The study demonstrated that berberine not only inhibited apoptosis and oxidative stress, but also enhanced synaptic activity and plasticity. Berberine, as a natural alkaloid compound, exhibits a variety of pharmacological effects. In recent years, numerous studies have explored the role of berberine in diseases of the central nervous system such as AD (Cheng et al., 2022; Yuan et al., 2019). The enrichment analysis we conducted by Mienturnet, has revealed that PPP2R5E is a gene target of miR-132-3p. The PPP2R5E gene is important for the phosphorylation of tau protein, and it is involved also in the Wnt/β-catenin pathway. In addition, the berberine-induced up-regulation of miR-132a-3p could potentially influence the expression of the PPP2R5E gene and the pathways in ~~where~~ which it is involved in. For this reason, modulation of miR-132-3p through berberine administration~~, represent~~ represents a potential therapeutic approach in AD. On the other hand, a recent study has revealed that miR-22-3p, found to be downregulated in AD, enhances apoptosis and reduces amyloid-β (Aβ) deposition (Xia P. et al., 2022). It is suggested that curcumin leads to the upregulation of the above miRNA (miR-22-3p), modulating relevant genes and pathways (FRAT2 and Wnt/β-catenin pathway) in which this miR is involved in.

Conclusions

In conclusion, our *in silico* study~~,~~ performed i) a secondary analysis, through Minturnet interrogation of published data from different sources and ii) used the results obtained from the Minturnet analysis as input for the original Reactome interrogation. This allowed us to detect significant molecular pathways involved in AD. Furthermore, working ~~backwards~~backward, we identified the miRs that target the genes involved in the two identified pathways of interest (i.e. Wnt-beta catenin phosphorylation and Netrin-1). These miRs may themselves be modulated by BC. In addition to the findings presented in this study, the identification of gene-nutrient cross-talk interactions using the STITCH tool opens up promising new avenues for future research. Further exploration of these interactions may deepen our understanding of nutrient-gene dynamics in AD and lead to novel therapeutic strategies.

The rationale for such an approach is supported by the integration of independent studies and our novel analysis conducted with bioinformatic tools. Our *in silico* research paves the way for the use of data science, appropriate repositories, platforms, and bioinformatics algorithms for the therapeutic management of AD. The interest of this study was also to bring out BC able to restore the dysregulated miRs, genes, and pathways that have shown potential beneficial effect in the context of neurological diseases, in data from the literature, which may represent an adjunctive piece of interest. The analysis performed and the results obtained represent, to our knowledge, an original attempt to link results from different sources, such as biochemical, cellular, and animal model studies. The results and conclusions obtained are of interest and potentially useful for

further comprehensive investigations to fully explain the effects of BC in the context of neurological diseases.

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