In Silico Analysis to Link Insulin Resistance, Obesity and Ageing with Alzheimer’s Disease

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Abstract
The process of ageing accompanies several metabolic diseases. With ageing, fats accumulate to increase the visceral and abdominal adiposity leading to hyperinsulinemia, insulin resistance, obesity and several other diseases. Drosophila melanogaster is often used to study the ageing process and its related disorders. Therefore, in this study, we performed an in silico analysis to relate the process of ageing and insulin resistance. We analysed the data of insulin-resistant Drosophila from the GEO database and compared it with the data from the literature survey. We observed that 98 genes were common in both the models, and they showed gene modulations related to metabolic pathways, fatty acid metabolism, insulin resistance and neural receptor–ligand binding pathways. Analysis of the REACTOME database against human data revealed that the TRKB signalling pathway is commonly affected. The TRKB-mediated BDNF pathway is a major regulator of memory loss. We further analysed the common genes in Alzheimer's disease and compared the fly data with human data to identify the diseases related to these common genes. Then, we performed a literature survey to provide protective mechanisms for the TRKB signalling pathway activation, mediated through polyphenols. We treated the flies with sesamol-conjugated lipoic acid derivative (a phenolic compound) at hormetic doses to evaluate its effect on the memory of flies.

Keywords Ageing · Insulin resistance · Alzheimer’s disease · Drosophila · TRKB signalling · Phytocompounds · Neurological disorders · Memory

Introduction
Ageing is an irreversible process of multicellular organisms and unicellular organisms. The scientific community is researching and adding hypotheses to elaborate on the cellular and molecular machinery of ageing. Recent research in this field has made it progressively clear that ageing is due to the build-up of molecular damage, which gives a unified theory of ageing. Ageing is a process that predisposes metabolic imbalances like insulin resistance and oxidative stress that ultimately leads to age-related disorders like obesity, diabetes, neurological disorders and memory impairments (de la Monte 2017). For decades, drosophila has been used as a model organism to study ageing and age-related diseases. Drosophila melanogaster belongs to the genus drosophila of family Drosophilidae. This Drosophila genus contains about 1500 different species, and they have diversity in appearance, behaviour and breeding habitat. D. melanogaster has been widely used in genetic research and is a preferred model organism in developmental biology studies (Parvathi et al. 2009). Drosophila is the dominant model used to understand the development of an organism from an embryo to an adult. Many genes of drosophila are homologous to human genes and therefore studied to gain a better understanding of these genes in humans (Jennings 2011). Pathways like malonate–acetate, shikimic acid and isoprenoid are involved in polyphenol production. They have proven therapeutic effects against several pathological conditions, including neurodegenerative diseases (Stewart and Stewart 2008). Sesamol mitigates memory impairment and causes neuroprotection via activation of Nrf2, NFκB
and BDNF (Kumar et al. 2010; Liu et al. 2017, 2018; Ren et al. 2018). Therefore, in this study, we have tried to identify the common genes involved in ageing, insulin resistance and neurodegenerative diseases. We have also analysed the effect of a phenol-derived synthetic compound’s ability to mitigate age-related memory impairment.

Materials and Methods

Gene Expression Data

We have used the Gene Expression Omnibus (GEO) database to obtain Drosophila insulin-resistant obese samples and ageing samples data. We have analysed the dataset (GSE105448) for high-sugar–fed male Drosophila against normal diet–fed male Drosophila. These samples are insulin resistant and obese. We obtained ageing fly data from a literature survey on genetic responses towards mating and ageing in Drosophila (Zhou et al. 2014). We also used the dataset (GSE48681) for analyzing the Alzheimer’s disease (AD) model flies. In this data, we have utilized the 3-day-old fly data as young control flies and the 20-day-old fly data as aged diseased flies. The data up to 10% false discovery rate (FDR) only was used.

We have obtained the data from GEO database and literature to ensure their reliability. The data utilized for the in silico work has been collected from previously published works and is analysed through published and frequently used reliable end-user bioinformatics software.

Gene Ontology

Functional interpretation for each dataset was performed individually through DAVID (https://david.ncifcrf.gov/). It is a free online tool used for gene ontology studies (Dennis et al. 2003). Drosophila melanogaster was selected as the background, and all other parameters were kept in default mode. Venn diagram was also generated to deduce the overlap between the two datasets using InteractiVenn online tool. We explored the ageing dataset and insulin-resistant dataset to find the common genes.

Comparison with Human Data

The ageing and insulin resistant/obese datasets were individually uploaded to REACTOME database (https://reactome.org/) and searched against human data to analyse the pathways for regulation between Drosophila and humans. We compared the Alzheimer’s disease (AD) dataset with the insulin-resistant/obese data set to identify the common genes. Then, we subjected these genes to gene ontology analysis through DAVID and GeneMANIA (Warde-Farley et al. 2010) (https://genemania.org/). METASCAPE (Zhou et al. 2019) was used to compare the Drosophila data with human data (https://metascape.org/gp/index.html#main/step1). We searched the literature to obtain information on phytocompounds that can activate TRKB (tropomyosin receptor kinase B) signalling pathway. We have considered research articles and reviews within 5 years for the analysis.

Fly Husbandry and Diet Preparation

Wild-type Drosophila melanogaster flies (Canton-S) were reared at controlled temperature 25°± 1 °C and light/dark cycle (12:12 h). Flies were maintained in 300-ml polypropylene bottles containing 30 ml of maintenance diet (MM diet) (10% semolina (w/v), 10% jaggery (w/v), 1.5% agar (w/v), 3% methyl paraben (v/v) and 0.3% propionic acid (v/v) (Chattopadhyay et al. 2015). Eggs were collected and transferred to a new bottle. Newly emerging flies were segregated based on sex. Then, these flies were transferred to 2 different diets: (1) standard sucrose-yeast diet (SYD) (10% sucrose (w/v), 10% yeast extract (w/v), 2% agar (w/v), 3% methyl paraben (v/v) and 0.3% propionic acid (v/v) (Chattopadhyay et al. 2015) and (2) high-fat diet (HFD) (10% sucrose, 10% yeast extract, 2% palmitate, 2%Tween-80 and 1.5% agar, 3% methylparaben and 0.3% propionic acid). For sesamol-conjugated lipoic acid–derivative supplementation, the compound was dissolved in 0.5% DMSO and added into SYD and HFD at final concentrations of 30 µM and 60 µM by proper mixing. Standard control diets contained only water as a vehicle.

Memory Assay

Age-matched Drosophila flies were sorted into a group of 10 flies based on their sex for each set. An in-house T-maze apparatus was built, and a modified protocol from JOVE was used for this assay (Malik and Hodge 2014). All the experiments were conducted under dim red light to block the visual inputs for the flies. We introduced the flies to a training tube attached to the T-maze. They were then allowed to adapt to the tube and airflow for 2 min. Then, the first odour (yeast) was introduced in one of the arms of the T-maze with a 60-V shock (consisting of 1.25-s pulses with 3.75-s interpulse intervals) for a total duration of 1 min. We calculated the time with a stopwatch. While doing this, we attached only one arm and removed the other arm. We followed the same way while introducing the second odour. The flies were given a 30-s rest period and then introduced to the second odour (banana) for 60 s without any shock. Then again, we
gave a rest period of 30 s, and the flies were finally moved from the training chamber into the central chamber of the T-maze for 90 s. Then, both the tubes were fitted into the bottom of the apparatus to form the T-maze.

**Short-Term Memory Retention**

The flies were simultaneously exposed to both odours and were allowed to move towards them. The test was conducted for 120 s to allow maximum (80%) mobility. The memory retention analysis was recorded for 3 times with a gap of 10 min, and the average was utilized as the final result. We recorded the flies that avoided the punishing chamber odour against the total number of flies as the percentage of flies retaining short-term memory.

**Long-Term Memory Retention**

We trained batches of flies in 2 cycles of spaced training with a 6-h inter-cycle interval. Then, long-term memory was evaluated, 12 h after the training. Six-hour interval was considered because one-cycle training in *Drosophila* leads to the formation of a labile-phase of memory detected for up to 7 h.

**Results and Discussion**

**Gene and Genome Analysis**

*Drosophila* has served as a model organism for many human diseases and disorders due to its homology with *Homo sapiens*. We have analyzed the GEO database and published literature to obtain data for genomic comparison between ageing flies and insulin-resistant obese flies. Insulin resistance led by inflammation is the root cause of many metabolic diseases. Recently, insulin resistance has been marked as a characteristic feature of the normal ageing process. Normal ageing is accompanied by fat deposition and lipid accumulation in the abdomen and visceral compartments leading to age-enhanced insulin resistance or hyperinsulinemia (Ryan 2000; Refaie et al. 2006). The data obtained from the literature survey and GEO database revealed 482 genes that are differentially expressed during the process of ageing, and also insulin resistance during obesity leads to the modulation of 1267 genes. The datasets were analyzed for their gene ontologies (Supplementary data 1). We observed that the top-ranked biological process affected by the ageing process was cytoskeleton and synapse organisation, immune responses and metabolic processes. The gene ontology analysis of obese/insulin-resistant sample data revealed the modulation of receptor signals and signal transduction, synaptic transmissions and organization, cytoskeleton organisation and circadian rhythm entrainment. Most of the metabolic pathways, hippo signalling pathways, fatty acid biosynthesis-related pathways, cytokine-mediated pathways and neuronal receptor-ligand interacting pathways were regulated by the listed gene sets. We observed that the genes listed in ageing data and the gene list of insulin-resistant obese data had a few similarities based on their gene ontology. These similarities between these two datasets provoked us to investigate the common genes between these two datasets. Among the reported genes, 98 genes were common (Table 1) in both ageing as well as insulin-resistant conditions (Figs. 1 and 2).

Further, a comparison between the fly model and human in general was performed. The similarities within pathways were obtained by comparing the *Drosophila* genome with the human genome using REACTOME database (https://reactome.org/) (Fig. 1).

**Comparison with Human Data**

The datasets analysed through REACTOME database within the human genome display TRKB-mediated signalling pathway. Specifically, the pathways enhanced in age-related gene set show correlations to TRKB signalling pathways mediated through BDNF, NTF3 and NTF4 (Supplementary data 2a, 2b). In comparison, the high sugar–fed fly data from gene enrichment analysis revealed the involvement of GABA, NTF3, NTF4, TRKB and BDNF (Supplementary data 3). BDNF and other neurotropic factors NTF3 and NTF4 are essential players of neural plasticity and survival. When the axons of the distal segment of nerves degenerate due to damage in the peripheral nerves, the axons of the proximal segment start budding, which gradually grow and eventually form a connection with the target organ to restore its function. In the absence of NTF, the proximal segment begins to degenerate rapidly, and the cell body dies. BDNF mainly acts through the TRKB pathway and plays a vital role in learning and memory. TRKB acts as a receptor for the neurotropic ligand BDNF and NT4 (Moosavi et al. 2015). BDNF can also inhibit the phosphorylation of the GABA receptor (Xiao and Le 2016; Porcher et al. 2018; Xiang et al. 2019). Modulation in TRKB signalling and its transactivation can lead to neuronal damages. Therefore, proper TRKB signalling is required for learning and memory. This modulation is the cause of age-related neurodegenerative diseases observed in humans and *Drosophila*. Next, we analyzed data from Alzheimer’s disease (AD) to identify the common genes between insulin-resistant/obese flies and AD flies.

**The Relation Between Insulin Resistance/Obesity and AD**

The comparison between the datasets of AD and the insulin-resistant/obese model revealed that there is a significant number
of genes that commonly regulate both the diseases (Supplementary data 4). The functional annotation and the analysis of enrichment clusters for the standard gene sets revealed their involvement in the stimulus, metabolic, biosynthesis and synapse-related biological processes (Supplementary data 4; Fig. 3). The biological functions related to these common genes majorly included synaptic communication, reflexes towards the light, sound, mechanistic and abiotic stimulus (Table 2). When these common genes were analyzed against human data, many neurological diseases were predicted for this dataset (Fig. 4). There are genes that can commonly regulate and affect the occurrence/maintenance of both the diseases and might be associated with the ageing process also. Thus, we next attempted to search the literature for phytocompounds that might retard the ageing process and the related neurological disorders. Since our data showed the enrichment for TRKB-related pathway, we focused this survey on TRKB modulations.

### Phytochemical Survey

Our in silico analysis revealed the TRKB pathway as a link between insulin resistance/obesity, ageing and Alzheimer disease, targeted by the list of common genes. Alzheimer is a disease of memory loss, and the TRKB/BDNF pathway is an important pathway mediating neuronal plasticity and survival. This pathway has been reported to play an important role in controlling memory retention and progression of Alzheimer disease (Allen et al. 2011; Wang 2019). This pathway is modulated mainly by oxidative stress, Nrf2 and PI3K/AKT and ERK signalling. Therefore, our next attempt was to explore compounds that might enhance the activity of this pathway.

There are a few phytocompounds that can regulate both or any one of the molecules (TRKB, BDNF) (Hannan et al. 2020).

Phenols constitute a significant class of phytocompounds that are abundantly present and have proven therapeutic effects against several pathological conditions, including neurodegenerative diseases. Phenolic compounds produced via malonate–acetate pathway, the shikimic acid pathway and the isoprenoid pathway. The shikimic acid pathway yields three aromatic amino acids that are essential precursors of plant phenolics: tyrosine, tryptophan and phenylalanine. Phenylalanine converts to salicylic acid, cinnamic acid, p-coumaric acid, p-hydroxybenzoic acid, sinapic acid, caffeic acid and ferulic acid. The malonate–acetate pathway is similar to the fatty acid synthesis pathway. It involves sequential additions of malonyl-CoA to create a polyketide chain, which cyclizes to form a phenolic ring structure. Such structures like acetyl-CoA, malonyl-CoA and p-coumaric acid yield chalcone. Chalcone can undergo

| Table 1 | The genes that were observed to be differentially expressed among the ageing flies and the high-sugar–fed insulin-resistant obese flies are listed here as the common genes |
|----------------|-----------------|
| CG4213 | CG17633 |
| CG13947 | CG5853 |
| Lsp1beta | CG13138 |
| CG5080 | Pim |
| CG31928 | CG5096 |
| CG31926 | CG7300 |
| CG31661 | CG6724 |
| CG17239 | CG31869 |
| CG17234 | CG12517 |
| Send1 | CG16743 |
| CG31681 | CG14915 |
| CG3597 | Vm32E |
| Daw | Vha100-5 |
| Odd | CG5867 |
| Bsg25A | Vm34Ca |
| Ebla3 | CG16956 |
| CG3036 | CG31813 |
| Jon25Bii | Ance |
| Jon25Bii | NimB2 |
| Jon25Bi | CG43333 |
| CG14036 | Send2 |
| Qtc | CG31775 |
| CG14022 | CG42586 |
| CG14014 | CG15263 |
| Vm26Ab | CG15255 |
| Vm26Ac | CG15254 |
| Vm26Aa | CG15253 |
| Psd | CG7631 |
| CG13992 | CG6870 |
| Kr-h1 | ninaD |
| Tg | CG33120 |
| CG9527 | CG10623 |
| CG15818 | CG10650 |
| CG5958 | AMD |
| Uro | Fon |
| LKR | CG13084 |
| Tg | CG13083 |
| Mur29B | FBP |
| Peritrophin-15b | CG17571 |
| Peritrophin-15a | CG33510 |
| CG13091 | CG8677 |
| Tsp29Fa | CG7881 |
| Tsp29Fb | Cypr6w1 |
| Mco1 | CG1942 |
| CG13113 | CG12825 |
| CG13114 | Odc1 |
| CG3841 | Mal-A1 |
| Mal-A3 | Mal-A6 |
| Mal-A4 | Mal-A7 |
various modifications to produce a variety of isoflavones, flavanones, flavon-3-ols, flavones and anthocyanidins. Some phenolics are produced by combining the products from both the malonate–acetate and shikimic pathways. About 8000 different types of plant phenolics are known (Stewart and Stewart 2008) and characterized by the presence of repeated phenolic structural units. They are mainly of natural origin (from fruits, vegetables and spices), but they can also be produced synthetically, semi-synthetically or organically (as in beverages, chocolates and wines). Out of 8000 polyphenols, about 3000 are flavonoids in nature (Stewart and Stewart 2008). Other than flavonoids, there are phenolic acids, stilbenes and lignans that form the subset of polyphenolic compounds (Pandey and Rizvi 2009).

**Flavonoids**

Tea is rich in polyphenol content. Other than its antioxidant nature, they are reported being neuroprotective as well. They attenuate the inhibition of the TRKB/Akt signalling pathway and also restore the pro-BDNF expression in cytotoxic cells (Yang et al. 2020). Flavonoid 7, 8-DHF (7,8-dihydroxyflavone) targets the PI3-AKT-ERK/CREB pathway to upregulate TRKB dimerization and phosphorylation (Jang et al. 2010). This compound acts as an agonist for TRKB. The flavonoid, 7,8,3-trihydroxyflavone, produces similar effects by phosphorylating ERK and TRKB receptors (Yu et al. 2013). Another polyphenolic flavonoid, diosmetin, is capable of weakly inducing phosphorylation of TRKB (Moosavi et al. 2015). Flavanonol compound, astilbin, upregulates BDNF and activates ERK and Akt pathways (Lv et al. 2014).

**Non-Flavonoid Polyphenols**

The neuroprotective role of polyphenols is carried out by activating the pathways such as PKC-ERK1/2, PI3K/Akt, MAPK and Akt-ERK1/2, which regulate cell proliferation and growth, translation, transcription and survival. These polyphenols bind Trk receptors to activate the protein kinase cascades, CREB, and increase the expression of Bcl-xL, Bcl-2 and neurotropic factors like BDNF, NT4/5 and NT3.
and NGF (Huang and Reichardt 2003). A decrease in neurotropic factor is an indication of neurodegenerative diseases, characterizing its physiological attributes (Gupta and Sharma 2017). -tetrahydroxystilbene-2-O-β-D-glucoside (THSG) adapts the PI3/Akt signalling pathway to provide neuroprotective effects (Yang et al. 2014). Another stilbene, resveratrol, is capable of inducing the release of BDNF in a time-dependent and dose-dependent manner. Neuroprotective effect of resveratrol is hindered due to the blockage of neurotrophins (Zhang et al. 2012). Resveratrol, baicalein, and rosmarinic acid (a caffeic acid ester) also arbitrate BDNF-ERK-mediated neurotropic action (Moosavi et al. 2015). Another polyphenol, ferulic acid, also mediates the CREB-BDNF signalling pathway (Yabe et al. 2010). Chrysin also modulates BDNF production and scavenge-free radicals (Souza et al. 2015). Polyphenols such as curcumin target PI3K-Akt/CREB-ERK and insulin signalling pathways, thereby upregulating BDNF (Zhang et al. 2015). Topiramate increases BDNF expression and enhances the phosphorylation of TRKB (Mao et al. 2015). Polyphenol, harpagoside, regulates the PI3K-Akt-ERK pathway to enhance the activity and expression of BDNF (Li et al. 2015). Oleuropein, an olive-derived polyphenol was reported to increase the levels of BDNF and NGF levels in serum. Contradicting reports show reduced levels of BDNF in the hippocampus (Carito et al. 2014). Some phenolic compounds and non-phenolic compounds induce BDNF expression (Zhang and Tang 2006; Hoi et al. 2010; Zhang et al. 2011; Yuan et al. 2014; Gupta and Sharma 2017).

### Table 2

| Biological function                              | FDR          | Genes in network |
|--------------------------------------------------|--------------|------------------|
| Detection of light stimulus                      | 2.92E−07     | 14               |
| Phototransduction                                | 4.96E−07     | 13               |
| Detection of external stimulus                   | 5.07E−07     | 14               |
| Detection of abiotic stimulus                    | 5.07E−07     | 14               |
| Rhabdomere                                       | 1.37042E−05  | 10               |
| Response to light stimulus                       | 3.14106E−05  | 17               |
| Photoreceptor activity                           | 0.000216117  | 6                |
| Response to radiation                            | 0.000216117  | 17               |
| Cellular response to radiation                   | 0.009136754  | 8                |
| Sensory perception of sound                      | 0.013069066  | 9                |
| Cellular response to abiotic stimulus            | 0.027025423  | 8                |
| Cellular response to light stimulus              | 0.038283938  | 7                |
| Detection of visible light                       | 0.046789133  | 6                |
| Sensory perception of mechanical stimulus        | 0.055660088  | 9                |
| Synapse assembly                                 | 0.074724231  | 12               |
| Detection of stimulus                            | 0.083505031  | 15               |

### Memory Retention

Flies were treated with two different concentrations of sesamol-conjugated lipoic acid derivative (30 µM and 60 µM) with three different diets: maintenance diet (MD), high-fat diet (HFD), and normal sucrose yeast diet (SYD). In HFD, short-term memory retention increased after the exposure to sesamol-conjugated lipoic acid derivative (Fig. 5). As the
concentration increased, the retention was observed to have a gradual decrease in males. This indicates that up to a threshold point, the compound increases the memory retention in the Drosophila males. But it decreases after crossing the threshold level. However, in the case of females, it showed an increase in short-term memory retention, which increased gradually giving a positive response at all the concentrations. Thus, the threshold level of the compound is different for males and females.

But, in SYD, both males and females had an increase in short-term memory retention, due to the administration of the sesamol-conjugated lipoic acid derivative (Fig. 6). Therefore, the memory retention was better in flies fed with normal diet. The females showed better memory retention potential when compared to males. This is in accordance with the previously published data that states the difference in memory retention based on sexes. Many earlier studies have reported that females are better in memory retention as compared to males (Lowe et al. 2003; Loprinzi and Frith 2018). Our data also represents the same conclusion. Further, our data indicates that diet also plays a pivotal role in memory retention. High fat diet consumption is capable of reducing the memorizing capability, and also reduces the therapeutic effect of drugs that might aid in memory retention.
The flies retained their long-term memory at all the concentrations in both the diets even after 12 h. This indicates that the sesamol-conjugated lipoic acid derivative helps in retaining the memory at both short- and long-term durations. Deterioration in long-term memory retention is a physiological ailment in Alzheimer disease patients.

**Conclusion**

The TRKB-BDNF signalling pathway is known to regulate neurodegenerative diseases through a neuroprotective mechanism. Many factors can cause neurodegeneration, and ageing is one of the prominent factors. Neurodegeneration, memory loss, abdominal and visceral adiposity are characteristics of ageing. Specifically, hypertrophic adiposity is observed mostly in men (Palmer and Kirkland 2017). Men are also most vulnerable to diabetes and cardiac myopathies (Mancuso and Bouchard 2019). The data obtained from insulin-resistant obese male flies revealed that TRKB signalling is essential in reducing the effects of ageing and insulin resistance. Further, there are many phytochemicals which are used to treat neurological disorders by targeting TRKB signalling. They can be used to reduce the effects of ageing and insulin resistance. This is achieved by targeting the TRK receptors through activation of PI3K/Akt, ERK, CREB pathways, Nrf2 pathway and upregulation of antioxidant and detoxifying enzymes. In support of this observation, we also observed many genes, which are common between obesity-related insulin resistance and AD. These genes might be responsible for regulating both the diseases together. Insulin resistance is a well-known link between obesity and diabetes, but it is recently linked to AD (de la Monte 2009; Ferreira et al. 2018). These reports are consistent with our observations on bioinformatic analysis and Drosophila memory assay. The NGF and BDNF are early targets of the disease which ultimately leads to the symptoms of dementia and memory loss. BDNF/TRKB is a vital component of long-term memory potentiation (Allen et al. 2011; Wang et al. 2019). Since our compound is able to show enhanced long-term memory retention, we have attempted to relate this data to AD. We conclude that this data can be used as preliminary data to further investigate the pathway and molecular mechanisms adapted by this compound and establish it as a therapeutic agent for AD. We also hypothesize that this compound might be enhancing memory retention through BDNF/TRKB pathway. But a more insightful approach toward these genes might give a clear link between AD, ageing, insulin resistance and obesity. Also, a better understanding of the neurotropic effects and the molecular mechanisms of action for these compounds could help to design better dietary supplements to mitigate the effects of ageing.

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**Author Contribution** P.S, P.J, R.D, and K.T conceived, designed, and directed the study. P.J and R.D. conducted the synthesis. P.S, K.P, S.Y, S.D, and Y.S conducted the experiments with Drosophila. P.S and K.T were involved in writing and discussion of the manuscript.

**Data Availability** Data available on request.

**Declarations**

**Ethics Approval and Consent to Participate** This work did not require any ethics approval and consent to participate.

**Consent for Publication** The author consent is obtained.

**Competing Interests** The authors declare no competing interests.

**References**

Carito V, Venditti A, Bianco A et al (2014) Effects of olive leaf polyphenols on male mouse brain NGF, BDNF and their receptors TrkA, TrkB and p75. Nat Prod Res 28:1970–1984. https://doi.org/10.1080/14786419.2014.918977

Chattopadhyay D, James J, Roy D et al (2015) Effect of semolina-jaggery diet on survival and development of Drosophila melanogaster. Fly (austin) 9:16–21. https://doi.org/10.1080/19336934.2015.1079361

de la Monte SM (2017) Insulin Resistance and neurodegeneration: progress towards the development of new therapeutics for Alzheimer’s disease. Drugs 77:47–65. https://doi.org/10.1007/s40265-016-0674-0

de la Monte SM (2009) Insulin resistance and Alzheimer’s disease. BMB Rep 42:475–481. https://doi.org/10.5483/BMBRep.2009.42.8.475

Parvathi VD, Amritha AS, Paul SFD (2009) Wonder animal model for Genetic studies – D. melanogaster – Its lifecycle & breeding methods – a review. Sri Ramachandra J Med 2:33–38.

Dennis G, Sherman BT, Hosack DA et al (2003) DAVID: Database for Annotation, Visualization, and Integrated Discovery. Genome Biol 4. https://doi.org/10.1186/gb-2003-4-9-e60

Ferreira LSS, Fernandes CS, Vieira MNN, De Felice FG (2018) Insulin resistance in Alzheimer’s disease. Front Neurosci 12:1–11. https://doi.org/10.3389/fnnsc.2018.00830

Hannan MA, Dash R, Sohag AA, Haque M, Moon IS (2020) Neuro-protection against oxidative stress: phytochemicals targeting TrkB
signaling and the Nrf2-ARE antioxidant system. Front Mol Neurosci 13. https://doi.org/10.3389/fmoln.2020.00116

Hoi CP, Ho YP, Baum L, Chow AHL (2010) Neuroprotective effect of honokiol and magnolol, compounds from Magnolia officinalis, on beta-amyloid-induced toxicity in PC12 cells. Phytother Res 24:1538–1542. https://doi.org/10.1002/ptr.3178

Huang EJ, Reichardt LF (2003) Trk receptors: roles in neuronal signal transduction. Annu Rev Biochem 72:609–642. https://doi.org/10.1146/annurev.biochem.72.110101.161629

Allen SJ, Watson JJ, Dawbarn D (2011) The neurotransphins and their role in Alzheimer’s disease. Curr Neuropharmacol 9(4):559–573. https://doi.org/10.2174/157015911798376190

Jiang SW, Liu X, Yeper M et al (2010) A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. Proc Natl Acad Sci 107:2687–2692. https://doi.org/10.1073/pnas.0913572107

Jennings BH (2011) Drosophila—a versatile model in biology & medicine. Materials Today 14:190–195. https://doi.org/10.1016/S1369-7021(11)70113-4

Kumar P, Kalonia H, Kumar A (2010) Protective effect of sesamol against 3-nitropropionic acid-induced cognitive dysfunction and altered glutathione redox balance in rats. Basic Clin Pharmacol Toxicol 107:577–582. https://doi.org/10.1111/j.1742-7843.2010.00537.x

Li J, Ding X, Zhang R et al (2015) Harpagoside ameliorates the amyloid-β-induced cognitive impairment in rats via up-regulating BDNF expression and MAPK/P3K pathways. Neuroscience 303:103–114. https://doi.org/10.1016/j.neuroscience.2015.06.042

Liu Z, Chen Y, Qiao Q et al (2017) Sesamol supplementation prevents systemic inflammation-induced memory impairment and amyloidogenesis via inhibition of nuclear factor kappaB. Mol Nutr Food Res 61:1600734. https://doi.org/10.1002/mnfr.201600007

Liu Z, Liu X, Luo S et al (2018) Extract of sesame cake and sesame alleviates chronic unpredictable mild stress-induced depressive-like behaviors and memory deficits. Journal of Functional Foods 42:237–247. https://doi.org/10.1016/j.jff.2018.01.005

Loprinzi PD, Frith E (2018) The role of sex in memory test performance among children and adolescents. Arch Clin Neuropsychol 33(8):865–878. https://doi.org/10.1007/s00449-018-0023-2

Lv QQ, Wu WJ, Guo XL et al (2014) Antidepressant activity of astilbin: involvement of monoaminergic neurotransmitters and BDNF signal pathway. Biol Pharm Bull 37:987–995. https://doi.org/10.1248/bpb.b13-00968

Malik BR, Hodge JIL (2014) Drosophila adult olfactory shock learning. JoVE 3–7 https://doi.org/10.3791/50107

Mancuso P, Bouchard B (2019) The impact of aging on adipose function and adipokine synthesis. Front Endocrinol 10:1–12. https://doi.org/10.3389/fendo.2019.00137

Mao XY, Cao YG, Ji Z et al (2015) Topiramate protects against glutamate excitotoxicity via activating BDNF/TrkB-dependent ERK pathway in rodent hippocampal neurons. Prog Neuropharmacol Biological Psychiatry 60:11–17. https://doi.org/10.1016/j.pnpbp.2015.01.015

Moosavi F, Hosseini R, Saso L, Firuzi O (2015) Modulation of neurotrophic signaling pathways by polyphenols. Drug Des Devel Ther 10:23–42. https://doi.org/10.2147/DDDT.S96936

Palmer AK, Kirkland JE (2017) Aging and adipose tissue: potential interventions for diabetes and regenerative medicine. Physiol Behav 176:97–105. https://doi.org/10.1016/j.physbeh.2017.03.040

Pandey KB, Rizvi SI (2009) Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev 2:270–278. https://doi.org/10.4161/oxim.2.5.9498

Porcher C, Medina I, Gaiarsa JL (2018) Mechanism of BDNF modulation in GABAergic synaptic transmission in healthy and disease brains. Front Cell Neurosci 12:1–9. https://doi.org/10.3389/fncel.2018.00273

Refaie MR, Sayed-Ahmed NA, Bakr AM et al (2006) Aging is an inevitable risk factor for insulin resistance. Journal of Taibah University Medical Sciences 1:30–41. https://doi.org/10.1016/s1658-3612(06)70005-1

Ren B, Yuan T, Diao Z et al (2018) Protective effects of sesamol on systemic oxidative stress-induced cognitive impairments via regulation of Nrf2/Keap1 pathway. Food Funct 9:5912–5924. https://doi.org/10.1039/C8FF00143A

Ryan AS (2000) Insulin resistance with aging: effects of diet and exercise. Sports Med 30:327–346. https://doi.org/10.2165/00007256-200030050-00002

Gupta VK, Sharma B (2017) Role of phytochemicals in neurotrophins mediated regulation of Alzheimer’s disease. Int J Complement Altern Med 7:00231. https://doi.org/10.15406/ijcam.2017.07.00231

Souza LC, Antunes MS, Filho CB et al (2015) Flavonoid Chrysin prevents age-related cognitive decline via attenuation of oxidative stress and modulation of BDNF levels in aged mouse brain. Pharmacol Biochem Behav 134:22–30. https://doi.org/10.1016/j.pbb.2015.04.010

Stewart AJ, Stewart RF (2008) Phenols. In: Encyclopedia of Ecology. Elsevier, pp 2682–2689

Wang ZH, Xiang J, Liu X et al (2019) Deficiency in BDNF/TrkB neurotrophic activity stimulates δ-secretase by upregulating C/EBPβ in Alzheimer’s disease. Cell Rep 28(3):655-669.e5. https://doi.org/10.1016/j.celrep.2019.06.054

Wardle-Farley D, Donaldson SL, Comes O et al (2010) The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. Nucleic Acids Research 38(suppl_2), pp. W214–W220. https://doi.org/10.1093/nar/gkq537

Xiang J, Wang ZH, Ahn EH et al (2019) Delta-secretase-cleaved Tau antagonizes TrkB neurotrophic signalings, mediating Alzheimer’s disease pathologies. Proc Natl Acad Sci 116:9094–9102. https://doi.org/10.1073/pnas.1901348116

Xiao N, Le QT (2016) Neurotrophic factors and their potential applications in tissue regeneration. Arch Immunol Ther Exp 64:89–99. https://doi.org/10.1007/s00005-015-0376-4

Yabu T, Hirahara H, Harada N et al (2010) Ferulic acid induces neural progenitor cell proliferation in vitro and in vivo. Neuroscience 165:515–524. https://doi.org/10.1016/j.neuroscience.2009.10.023

Yang JR, Ren TT, Lan R, Qin XY (2020) Tea polyphenols attenuate staurosporine-induced cytotoxicity and apoptosis by modulating BDNF-TrkB/Akt and Erk1/2 signaling axis in hippocampal neurons. IBRO Reports 8:115–121. https://doi.org/10.1016/j.ibro.2020.04.002

Yang XP, Liu TY, Qin XY, Yu LC (2014) Potential protection of 2,3,5,4’-tetrahydroxyxilobene-2-O-β-d-glucoside against staurosporine-induced toxicity on cultured rat hippocampus neurons. Neurosci Lett 576:79–83. https://doi.org/10.1016/j.neulet.2014.05.045

Yu Q, Chang Q, Liu X et al (2013) Protection of spiral ganglion neurons from degeneration using small-molecule TrkB receptor agonists. J Neurosci 33:13042–13052. https://doi.org/10.1523/JNEUROSCI.0854-13.2013

Yuan X, Yang L, Yang Z et al (2014) Effect of nigranonic acid on Ca2+/ influx and its downstream signal mechanisms in NGF-differentiated PC12 cells. J Ethnopharmacol 153:725–731. https://doi.org/10.1016/j.ejep.2014.03.038

Zhang C, Tian X, Luo Y, Meng X (2011) Ginkgolide B attenuates ethanol-induced neurotoxicity through regulating NADPH oxidases.
Zhang F, Wang Y, Liu H (2012) Resveratrol produces neurotrophic effects on cultured dopaminergic neurons through prompting astroglial BDNF and GDNF release. Evid-Based Complement Altern Med. https://doi.org/10.1016/j.tox.2011.06.006

Zhang HY, Tang XC (2006) Neuroprotective effects of huperzine A: new therapeutic targets for neurodegenerative disease. Trends Pharmacol Sci 27:619–625. https://doi.org/10.1016/j.tips.2006.10.004

Zhang L, Fang Y, Xu Y et al (2015) Curcumin improves amyloid β-peptide (1–42) induced spatial memory deficits through BDNF-ERK signaling pathway. PLoS ONE 10:e0131525. https://doi.org/10.1371/journal.pone.0131525

Zhou S, Mackay TF, Anholt RR (2014) Transcriptional and epigenetic responses to mating and aging in Drosophila melanogaster. BMC Genomics 15. https://doi.org/10.1186/1471-2164-15-927

Zhou Y, Zhou B, Pache L et al (2019) Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. Nat Commun 10(1). https://doi.org/10.1038/s41467-019-09234-6

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