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Beneficial Fruit-Derived Phytochemicals in Treating Alzheimer's Disease – A Review

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ABSTRACT

Fruits, as a major source of nutrition have been investigated for their emerging evidence of several neuroprotective activities beneficial to Alzheimer's disease (AD). This paper discusses recent evidence suggesting several fruit-derived bioactive substances that possess anti-AD activity. The original articles from 2011–2022 were collected from Pubmed and Scopus with related keywords and filtered. Several fruit constituents have shown significant inhibitory action against β-amyloid and tau hyperphosphorylation, either directly or indirectly via secretase inhibition. Some were also found to be cholinesterase inhibitors with specific antioxidative roles, disruptors of the neuroinflammation system, and promoters of neurogenesis and the neurogenic process. Many fruit phytochemicals remarkably alter the capability defects shown in AD animal models, such as catechin, nobiletin, and alpha-mangostin. Therefore, further investigations exploring a certain bioactive isolate or formulated dosage form and its mechanism of action are necessary to provide effective prevention and supplementary treatment for AD.

INTRODUCTION

Fruits have always been an essential ingredient in human daily diets. Fruits, either eaten raw or processed, are known to be the primary source of nutrition, including vitamins, minerals, and fibers. Dietary habits with fewer fruits are correlated with dementia and Alzheimer's disease (AD) risk for the following 10 years (Francis et al., 2022). Recent studies have shown bioactive substituents derived from fruits to yield neuroprotective activity, promising to be developed as functional diets for AD (Sato et al., 2022). In addition, enriching daily intake with fruits may be beneficial to prevent various neurological or neurodegenerative disorders-related functional damage, especially in AD.

The hallmark of AD includes the gradual buildup of clusters of senile plaque and neurofibrillary tangles mediated by β-amyloid peptide and hyperphosphorylated tau aggregation, eventually causing neuronal injury and dementia (Tang et al., 2018). It also involves a significant decline in the neurotransmitter acetylcholine in synapses, the neuroinflammation process, and oxidative stress, leading to oxidative damage and neuronal death (Currò et al., 2016; Moniruzzaman et al., 2015; Suttisansanee et al., 2020). Notably, modulation of all the abnormalities has been the breakthrough in reversing AD conditions.

Several fruit bioactive components have shown promising anti-AD activity, from targeting Aβ peptide (Wen et al., 2020) to almost generally regulating the neurogenesis system and providing neuroprotection in the central nervous system (Bae et al., 2016).

There has been massive advancement in AD-related studies. However, evidence regarding fruit-derived phytochemicals to play against AD and its comprehensive discussions are limited. Therefore, this paper summarizes recent studies with scientifically proven anti-AD activity of fruit constituents to grow interest in developing fruit-based anti-AD supplementary treatments.

METHODS

This narrative review was written according to the original articles available in the Scopus and PubMed databases. The keywords used were “fruits,” “berry,” “Alzheimer’s,” and “neurogenesis.” The criteria for the articles to be included were common edible fruit-based studies that explored the potential neuroprotective bioactivity of fruit-derived extracts or isolates. Articles published in 2011–2022 were collected and filtered based on the criteria. The diagram of this method is summarized in Figure 1.

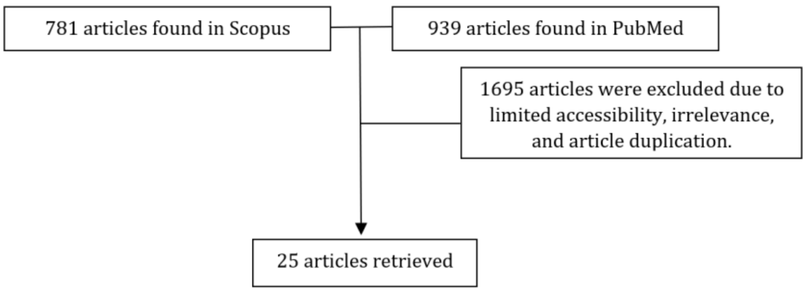

Figure 1. Resume of screening method

RESULTS AND DISCUSSION

Fruit-derived β-amyloid plaque and tau hyperphosphorylation inhibitors

The generation of neurotoxic β-amyloid (Aβ) in AD originates from a single transmembrane protein known as an amyloid precursor protein (APP) undergoing cleavage by β-secretase and γ-secretase, bringing up the stimulation of the amyloidogenic process (Roda et al., 2022). Each fruit may contain diverse phytochemicals capable of inhibiting Aβ plaque. Goji berry (*Lycium barbarum*) isolated pectin polysaccharide and flavonoid-rich extract reduce Aβ production in cell lines with APP overexpressed and nematode, respectively (Liu et al., 2020; Tang et al., 2018). Pectin also possesses β-site APP cleaving enzyme 1 (BACE1) and sAPPβ modulatory action and increases ADAM10 in SHSY5Y cell lines, which all lead to a non-amyloidogenic process (Zhou et al., 2018). Among carotenoids, lutein has been reported as the most functional carotenoid in apricot fruit (*Prunus armeniaca* L.) to block Aβ fibril formation (Katayama et al., 2011). These activities have been proven to improve neurobehavioral deficits in AD models (Du et al., 2019; Wen et al., 2020). The phenolic-containing methanolic extract of Romina strawberry is also able to reduce Aβ aggregation associated with reduced paralysis in the Caenorhabditis elegans model of AD (Navarro-Hortal et al., 2022).

Being a component of microtubules, tau protein undergoes phosphorylation as one of the posttranslational modifications. The neuronal loss in neurodegenerative patology often coexists with the aggregation of phosphorylated tau, which forms neurofibrillary tangles (NFTs) (Roda et al., 2022). Lychee (Litchi chinensis) seed’s polyphenol-rich fraction exerts both Aβ and tau hyperphosphorylation inhibition activities. This mechanism was observed in both cell lines (Tang et al., 2018; Xiong et al., 2020) and the rat hippocampus (Sun et al., 2020). The bioactive polyphenol substances are found to be catechin, procyanidin A1, and procyanidin A2 (Xiong et al., 2020). Tau hyperphosphorylation appeared as a consequence of Aβ (Roda et al., 2022). Some believe it is triggered by insulin receptor substrates (IRS) downregulation, reducing phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) signaling, and the opposite stimulation on the glycogen synthase kinase 3β (GSK-3β) pathway. Notably, Aβ accumulation is one of the underlying processes of IRS-1/PI3K/Akt pathway dysregulation (Sun et al., 2020). Thus, multi-targeted constituents may generate greater neuroprotection in AD models. Comparable results in animal models were also shown in commercially prepared eriodictyol and flavonoids-rich citrus fruits, which manage to suppress Aβ and overphosphorylated tau, reversing the cognitive defects in APP/PS1 transgenic mice (Li et al., 2022). This review shows the related anti-AD activity of bioactive resources found in many other fruits (Table 1).

Table 1. β-amyloid and Tau Hyperphosphorylation Inhibitors Derived from Fruits

Fruits	Compounds	Effect	Reference
Goji berry (*Lycium barbarum*)	Pectin	1. Downregulate $A\beta_{42}$ production in APP-overexpressed CHO/APPBACE1 and HEK293-APPsw cells. 2. Reduce BACE1 and sAPPβ and increase $A\beta_{42}$ degradation.	Zhou et al., 2018
	Flavonoid-rich extract	Downregulate Aβ in the transgenic Aβ-expressing nematode	Liu et al., 2020
Black chokeberry (*Aronia melanocarpa*)	Anthocyanin	Reduce neurotoxicity induced by $A\beta_{1\text{-}40}$ in the rat hippocampus	Wen et al., 2020
Black mulberry (*Morus nigra*)	Phenolic and anthocyanin aqueous extract	1. Reduce Aβ peptide neurotoxicity both in PC12 neuronal cells at 200 µg/mL and in the *Drosophila* model of AD. 2. Inhibit BACE1 after 28 days at 250 µg/mL and 500 µg/mL in fly larvae.	Suttisansanee et al., 2020
Apricot (*Prunus armeniaca L.*)	Carotenoid fraction	1. Inhibit Aβ fibril formation and maintain its destabilization (fraction). 2. Inhibit Aβ fibril formation with IC_{50} 9.1 µg/mL (lutein).	Katayama et al., 2011
Mango (*Mangifera indica*)	Mangiferin (leaves and bark fruit)	reduce $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ but not APP in aging senescence-accelerated mouse-prone 8 hippocampi	Du et al., 2019
Lychee (*Litchi chinensis*)	Polyphenol-rich fraction (seeds)	1. Reduce tau hyperphosphorylation in insulin-resistant cell lines by upregulating IRS-1/PI3K/Akt signaling. 2. Reduce activated BV-2 cells treated with $A\beta_{1\text{-}42}$.	Tang et al., 2018; Xiong et al., 2020
	Bioactive fraction (seeds)	Increase Akt and decrease GSK-3β and tau protein in the hippocampal CA1 area of an AD rat model.	Sun et al., 2020
Maypop (*Passiflora incarnata*)	Ethanolic extract (fruits and leaves)	Decrease p-tau/tau level in normal rats and sleep disorder in mice model	Kim et al., 2019
Citrus fruits	Eriodictyol (commercial)	Reduce Aβ agregation and p-tau in the APP/PS1 AD mouse model	Li et al., 2022

Fruit-derived AChE and BchE inhibitors

Alzheimer's disease pathology has also been correlated with a major loss of cholinergic neurons and acetylcholine neurotransmitters. Therefore, inhibition of acetylcholine-degrading enzymes, cholinesterases, which consist of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), may reverse this condition (Bilen et al., 2022). Table 2 shows recent studies exploring fruit-derived bioactive constituents having AChE and BChE inhibitory actions. The methanolic extract, originated from the fruit of *Phyllanthus acidus*, also known as gooseberry, has shown a concentration-dependent inhibition of AChE extracted from rat brains and BChE extracted from human blood (Moniruzzaman et al., 2015). Aqueous extract of mulberry (*Morus nigra*) "Chiang Mai," containing both phenolic and anthocyanins, inhibits AChE and BChE in addition to its Aβ and BACE1 inhibition properties (Suttisansanee et al., 2020).

Table 2. AchE and BchE Inhibitors Derived from Fruits

Fruits	Compounds	Effects	Reference
Gooseberry (*Phyllanthus acidus*)	Methanolic extract	Inhibit rat brain AChE and human blood BChE with IC_{50} values of 1009.87 μg/mL and 449.51 μg/mL, respectively.	Moniruzzaman et al., 2015
Black mulberry (*Morus nigra*)	Phenolic and anthocyanin aqueous extract	Inhibit AChE and BchE in vitro with 55.36% and 81.43% inhibition, respectively.	Suttisansanee et al., 2020
Pomegranate (*Omani pomegranate*)	Chloroform extract (peel)	1. Inhibit AChE at 100 μg/mL with 59.69% inhibition. 2. small binding energy to AChE (catechin)	Khokar et al., 2021
Peach (*Prunus persica*)	Metanol extract (fruit and peel)	"Morsiani 90" varieties inhibit AChE with IC_{50} of 67 mg/mL (fruit) and 60 mg/mL (peel).	Mihaylova et al., 2021
Grape (*Vitis vinifera*)	Anthocyanin-rich extract (grape skin)	Inhibit AChE with an IC_{50} of around 363.61 μg/mL.	Pervin et al., 2014
Mandarin melon berry (*Cudrania tricuspidate*)	Fruit extract	1. Inhibit AChE in PC12 cells and mouse hippocampus. 2. Increase Ach in scopolamine-induced learning and memory impairment in mice blood.	Jee et al., 2020
Palm fruit (*Elaeis guineensis*)	Water-soluble palm fruit extract	Inhibit AChE and BChE with an IC_{50} around 0.218 ± 0.029 μg/mL and 222.860 ± 5.777 μg/mL, respectively.	Leow et al., 2021
Citrus (mainly *Citrus auratium* and *Citrus medica*)	Naringin (commercial)	Suppress brain AChE activity in psychosocially defeated stress-induced mice brain.	Oladapo et al., 2021
Lemon (*Citrus limoni)*	Lemon essential oil	Reduce AChE expression in the hippocampus of APP/PS1 mice	Liu et al., 2020

The anti-AD bioactive components are not limited to polyphenols and polar substances. The chloroform extract of Omani pomegranate fruit peel has shown greater AChE inhibition than butanol solvent despite its higher total phenolic and flavonoid content with superior antioxidant activity (Khokar et al., 2021). Therefore, this action may be affected by interactions between the mixed constituents. Furthermore, the effectiveness can vary between varieties, as demonstrated in metabolomic studies of eight varieties of peach (Prunus persica). Among them, the peel extract of the "Morsiani 90" variant displays the highest inhibition of the AChE enzyme with IC50 scores of 60 mg/mL, while the lowest, "Flat Queen," scores 487 mg/mL (Mihaylova et al., 2021). The ethyl acetate fraction of water-soluble palm (Elaeis guineensis) oil extract has been reported to yield better inhibition of both AChE and BChE than the other fractions in vitro (Leow et al., 2021).

Several in vivo studies also achieved remarkable results. Common citrus fruits' (*Citrus auratium* and *Citrus medica*) flavonoid, naringin (4′,5,7 trihydroxy flavanone 7-rhamnoglucoside), showed an AChE inhibition of upregulated enzyme activity in stress-induced mice (Oladapo et al., 2021). Inhalation of lemon fruit (*Citrus limoni*)-extracted essential oil has also been found to reduce AChE as well as amyloid peptide in the hippocampus of APP/PS1 mice. This series of activities, along with Bdnf enhancement, are believed to deal with the memory loss in AD (Liu et al., 2020). These findings are promising to be developed in the form of functional foods or supplementary treatments for AD.

Fruit-derived antioxidant in Alzheimer's Disease

Excessive reactive oxygen species (ROS) are the major cause of oxidative stress-induced oxidative damage, including neurodegenerative diseases such as AD. The insufficient antioxidative system in the body to deal with the overproduction of ROS requires the consumption of supplementary antioxidant resources (Ghasemi-Tarie et al., 2022). In addition to its specific anti-AD activity as stated above, several fruit-derived bioactive substances also exert antioxidant properties, as shown by some recent studies as shown in Table 3.

An in vitro-based study of an aqueous extract derived from mulberry (*Morus nigra*) "Chiang Mai" containing both phenolic and anthocyanins demonstrated antioxidant activity and neuroprotection against H2O2-induced oxidative stress in PC12 neuronal cells. This was observed along with Aβ and cholinesterase inhibition (Suttisansanee et al., 2020). In addition to Aβ down-regulation activity, the purified flavonoid-rich extract of Goji berry (*Lycium barbarum*) is also able to promote anti-aging genes including Ins-18, Daf-16, Let-60, and Sir-2.1, as well as antioxidant enzymes Sod-1 and Skn-1 in the Caenorhabditis elegans model (Liu et al., 2020). As previously stated, an extract of grape skin (*Vitis vinifera*) rich in anthocyanins given at a dose of 50 mg/kg for 30 consecutive days elevated the antioxidant enzymes Sod, Cat, and GPx in the serum, liver, and brain of female Balb/c mice (Pervin et al., 2014). A polyphenolic xanthone in the pericarp of mangosteen (*Garcinia mangostana*), known as alpha-mangostin, has been able to fight against ROS by reversing antioxidant CAT and SOD2 in human SH-SY5Y neuroblastoma cells, which are assumed to target the SIRT1 active site, a deacetylase for neuroprotective proteins (Ruankham et al., 2022). Citrus fruit peels contain nobiletin (3′,4′,5,6,7,8-hexamethoxyflavone), which attenuates ROS and neuroinflammatory cytokines in the hippocampus of Aβ-induced AD mice (Ghasemi-Tarie et al., 2022).

Table 3. AD-related Antioxidant Derived from Fruits

Fruits	Compounds	Effects	Reference
Goji berry (*Lycium barbarum*)	Flavonoid-rich extract	Exert antioxidant activity and promote anti-aging *Ins-18*, *Daf-16*, *Let-60*, and *Sir-2.1* transcripts in the *Caenorhabditis elegans* model	Liu et al., 2020
Gooseberry (*Phyllanthus acidus*)	Methanolic extract	antioxidant feature with IC_{50} values of 15.62 μg/mL	Moniruzzaman et al., 2015
Black chokeberry (*Aronia melanocarpa*)	Isolated and purified anthocyanins	antioxidant properties with EC_{50} values of 0.83 g/L	Wen et al., 2020
Black mulberry (*Morus nigra*)	Aqueous extract containing phenolic and anthocyanin	Reduce H_2O_2-induced oxidative stress.	Suttisansanee et al., 2020
Grape (*Vitis vinifera*)	Anthocyanin-rich extract (grape skin)	Elevate antioxidant enzymes, SOD, CAT, and GPx, in the serum, liver, and brain of female Balb/c mice.	Pervin et al., 2014
Mangosteen (*Garcinia mangostana*)	Alpha-mangostin (pericarp) (commercial)	1. Suppress ROS production in H_2O_2-induced human SH-SY5Y neuroblastoma cells 2. Maintain antioxidant enzymes, CAT and SOD2, in H_2O_2-induced human SH-SY5Y neuroblastoma cells.	Ruankham et al., 2022
Citrus fruits	Nobiletin (peels) (commercial)	Attenuate ROS in $A\beta_{1-40}$-induced AD mice hippocampus	Ghasemi-Tarie et al., 2022

Fruit-derived neuroinflammation and neurogenesis modulator in Alzheimer's Disease

Chronic neuroinflammatory transduction in the central nervous system is mediated by pro-inflammatory cytokines produced by microglial cells and astrocytes. This activity contributes to the pathology of neurodegenerative disorders such as AD (Uddin and Lim, 2022). Many anti-inflammatory agents have been widely investigated for their mechanisms, such as curcumin, a polyphenol derived from *Curcuma longa* L. (Yuniarti et al., 2012). Recent studies have shown fruit-derived modifying substances to fight against the inflammation systems in the brain. Flavonoid-rich extracts of *Citrus bergamia* juice have been reported to exert neuroprotection via inhibition of neuroinflammation. In vitro studies in Aβ1-42-induced THP-1 monocytic cells have demonstrated the significant prevention of intracellular ROS and pro-inflammatory cytokine production for IL-6 and IL-1β. The mechanisms involved were found to be MAPK signaling enzymes and AP-1 transcription factor DNA binding inhibition, which both play roles in pro-inflammatory response regulation (Currò et al., 2016). The anti-Aβ polyphenol fraction of

Litchi chinensis, containing catechin and procyanidin A2, reverses neuroinflammation by reducing protein expression of TNF-α, IL-1β, and iNOS (Tang et al., 2018). Not only in its polyphenol constituents, downregulation of the NF-κB pathway and neuroinflammation was also observed in isolated saponins, as it significantly reduced the mRNA level of NF-κB p65 in Aβ25-35-induced PC12 cells, and the mechanism is concentration-dependent (Wang et al., 2017).

In addition to hindering neuroinflammation, promoting neurogenesis also contributes to the neurodegenerative condition. Neurogenesis is a cascade of regenerating mature neurons from neural stem cells. Neurodegeneration such as AD has been related to aging and cognitive declines, with concomitantly decreasing neurogenesis (Bae et al., 2016). Mandarin melon berry (*Cudrania tricuspidate*) fruit extract containing 4'-O-methylpinumisoflavone, 6,8-diprenyl orobol, 6,8-diprenyl genistein, and alpinumisoflavone exerts AChE inhibitory activity as well as neurogenesis and neuronal cell differentiation activation by elevating secreted phosphoprotein1 (Spp1) and kallikrein-related peptidase 6 (Klk6) genes. The recovery is also characterized by improved learning and memory function in the mouse model (Jee et al., 2020). Therefore, promoting neurogenesis may have a positive effect on AD. Neurogenesis modulatory activities have also been shown in the ethanolic extract of tomato (*Lycopersicon esculentum*), which can increase doublecortin (Dcx), an immature neuron marker, in the dentate gyrus of aged mice. It is also able to increase the synaptic plasticity marker brain-derived neurotrophic factor (Bdnf) and activate downstream ERK/CREB signaling in the hippocampus. This has been the proposed underlying mechanism for cognitive improvement based on a neurobehavioral study (Bae et al., 2016). In addition to inhibiting tau hyperphosphorylation, the ethanolic extract of *Passiflora incarnata* fruit and leaves promotes neurogenesis by increasing Dcx-positive cells, proliferating Ki67-positive cells, and Bdnf in the sleep disorder mouse model. Among the four analyzed extract components, including isoorientin, orientin, vitexin, and isovitexin, vitexin (apigenin-8-C-glucoside) is identified as the key neuroprotective agent to reverse AD-related sleep disturbance conditions (Kim et al., 2019). Recent evidence supporting this issue is shown in Table 4.

Table 4. AD-Related Neuroinflammation and Neurogenesis Modulator Derived from Fruits

Fruits	Compounds	Effects	Reference
Lychee (*Litchi chinensis*)	Polyphenol-rich fraction (seeds)	Reverses neuroinflammation by reducing TNF-α, IL-1β, and iNOS in $A\beta_{1-42}$ treated BV-2 cells	Tang et al., 2018
	Isolated saponins (seeds)	Downregulate *NF-κB p65* in $A\beta_{25-35}$-induced PC12 cells in a concentration-dependent manner.	Wang et al., 2017
Bergamot orange (*Citrus bergamia*)	Flavonoid-rich-juice extract	Prevent *IL-6* and *IL-1β* production at 0.1 mg/mL in $A\beta_{1-42}$ induced THP-1 monocytic cells.	Currò et al., 2016
Tomato (*Lycopersicon esculentum*)	Ethanolic extract	1. Improve cognitive performance on novel object recognition tests in aged mice 2. Increased Dcx+ cells, PSD95, Bdnf, p-ERK, and p-CREB in aged mice hippocampus 3. Decreased corticosterone in aged mice's hippocampus	Bae et al., 2016
Mandarin melon berry (*Cudrania tricuspidate*)	Fruit extract	1. Reverse p-CREB and p-ERK1/2 downregulation in PC12 cells 2. Improve spatial memory and fear learning memory via the Barnes Maze Test and the Fear Conditioning Test. 3. Increase *Spp1* and *Klk6* in scopolamine-induced learning and memory impairment in mice model.	Jee et al., 2020
Maypop (*Passiflora incarnata*)	Ethanolic extract (fruits and leaves)	Increased Dcx+ cells, Ki67+ cells, and Bdnf in sleep disorders in mice model.	Kim et al., 2019

CONCLUSIONS

To summarize, several fruit-derived phytochemicals and their assumed targets are shown in Figure 2. These phytochemicals combat AD in countless ways. Catechin and procyanidin A2 polyphenols in fraction mixtures counter Aβ peptide and tau hyperphosphorylation as well as neuroinflammation. A polyphenolic xanthone, apha-mangostin, with nobiletin, acts against oxidative stress. Meanwhile, the flavonoid naringin inhibits the AChE enzyme, maintaining cholinergic signals in the brain. In addition, several compounds, such as vitexin and isoflavones, support neural regeneration by inducing neurogenesis cascades. Well-established multi-targeting compounds found in fruits, either alone or combined, may perform better in reversing AD. Still, further experimental studies should be executed to carry out AD prevention and treatment as effectively as possible.

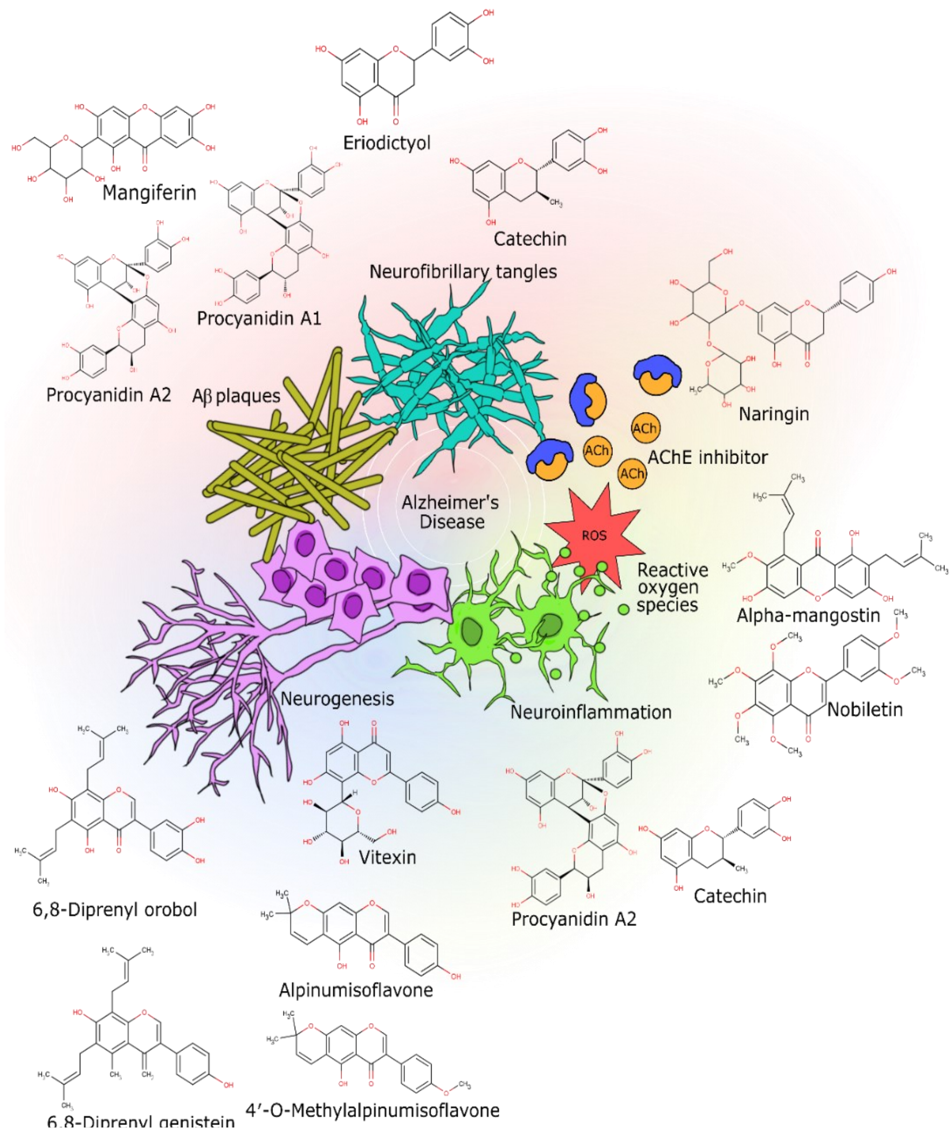

Figure 2. Common fruit-derived compounds have been found to potentially reverse Alzheimer's disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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