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Published online: 01 Jun 2022.

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REVIEW

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A comprehensive review on the prevention and regulation of Alzheimer's disease by tea and its active ingredients

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ABSTRACT

Alzheimer's disease (AD) has brought a heavy burden to society as a representative neurodegenerative disease. The etiology of AD combines multiple factors, concluding family, gender, head trauma, diseases and social psychology. There are multiple hypotheses explaining the pathogenesis of AD such as β-amyloid (Aβ) deposition and tau hyperphosphorylation, which lead to extracellular amyloid plaques and neurofibrillary tangles in neurons. The existing therapeutic drugs have several disadvantages including single target, poor curative effect, and obvious side effects. Tea contains many bioactive components, such as tea polyphenols (TPP), L-theanine (L-TH), tea pigment, tea polysaccharides and caffeine. The epidemiological investigations have shown that drinking tea can reduce the risk of AD. The mechanisms of tea active ingredients in the prevention and regulation of AD includes reducing the generation and aggregation of Aβ; inhibiting tau aggregation and hyperphosphorylation; inhibiting neuronal apoptosis and regulate neurotransmitters; relieving oxidative stress and neuroinflammation as well as the regulation of intestinal flora. This review summarizes the different signaling pathways that tea active ingredients regulate AD. Furthermore, we propose the main limitations of current research and future research directions, hoping to contribute to the development of natural functional foods based on tea active ingredients in the prevention and treatment of AD.

HIGHLIGHTS

- Natural AD-modulating active ingredients in tea have been summarized.
- Influences of drinking tea or tea active ingredients on AD are reviewed.
- Main regulating mechanisms of tea active ingredients on AD are explained.
- The main limitations of current research and future directions are proposed.

Introduction

More than 55 million people worldwide suffer from dementia, and it is predicted to reach 78 million by 2030 (Alzheimer's Disease International 2021). AD accounts for 80% of dementias (Anand, Gill, and Mahdi 2014). According to the estimation of Alzheimer's Disease International (ADI), three-quarters of people with dementia are undiagnosed, and the proportion may be as high as 90% in some low- and middle-income countries (Alzheimer's Disease International 2021). It is estimated that about 5 million people aged 65 years or older and 200,000 people under the age of 65 are affected by AD. The total estimated prevalence is projected to be 13.8 million by 2050 (Shal et al. 2018). The occurrence of AD is affected by many innate and acquired factors (Figure 1), but its pathogenesis has not been fully elucidated. Presently, the theories explaining the pathogenesis of AD mainly include protein misfolding (including Aβ and tau protein), oxidative stress, inflammation, ApoE4, adenosine, cholinergic hypothesis, glutamatergic hypothesis, endoplasmic reticulum stress, changes in calcium

metabolism and mitochondrial cascade hypothesis (Luo et al. 2021; Anand et al. 2017). The conventional therapeutic treatment of AD uses compounds that inhibit acetylcholinesterase (such as donepezil and rivastigmine) to increase the levels of acetylcholine in the nervous tissue of the brain. Recently, another drug for AD has emerged, memantine, which is a glutamatergic antagonist that protects neural tissue from glutamate-mediated excitotoxicity. Nevertheless, these drugs only relieve symptoms and there is no appropriate treatment to cure AD (Shal et al. 2018; Anand et al. 2017). Therefore, some studies tended to explore new theories to explain the causes of AD or to modify the previous hypotheses (Bostancıklıoğlu 2019; Chhatwal et al. 2022; Swerdlow, Burns, and Khan 2014).

Considering the difficulty of developing effective drugs along with their side effects, the potential of natural products for preventing and ameliorating AD has aroused extensive interest, which has been proved by both epidemiological and experimental evidence. Eskelinen et al. (2009) pointed out that drinking 3–5 cups of coffee daily in middle age could reduce the risk of AD later in life. The consumption
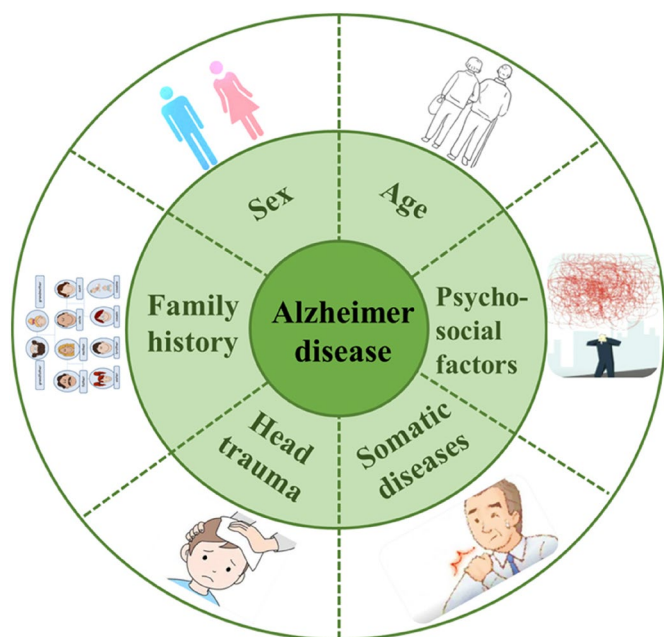
Figure 1. Main factors that affect Alzheimer's disease.

of ginkgo biloba extract improved cognitive assessment, daily living, and social behavior (Le Bars, Kieser, and Itil 2000). A 12-month clinical investigation revealed that an aloe-polymannose complex improved cognitive and immune function in adults with AD (Bokelmann 2022). Some fruits and plant-derived substances, such as apples, blueberries, grapes (Z. Yang, Ren, et al. 2021), curcumin (Reddy et al. 2018), quercetin (Bahar, Kim, and Yoon 2017), resveratrol (Yazir et al. 2015), naringenin (Shal et al. 2018) and lycopene (Przybylska 2020) have also been shown to alleviate neuroinflammation and delay the progression of AD. As one of the natural products, tea has also been widely explored for its therapeutic potential for AD (Prasanth et al. 2019; Shu-Qing Chen et al. 2018; Akbarialiabad et al. 2021). Tea has shown potent antioxidant and anti-inflammatory effects capable of modulating multiple targets in AD pathogenesis.

As the most consumed beverage in the world, tea was originated in China. Since ancient times, tea has been regarded as a both medicinal and edible plant that can improve or prevent various diseases. Over 30 countries are producing different kinds of tea as a natural beverage for relaxation and health. The functional components in tea include tea polyphenols, tea polysaccharides, amino acids, caffeine, tea pigments, amino acids and pyrroloquinoline Quinone (PQQ) (Wei et al. 2022). The content of these different natural active ingredients varies to different degrees according to the variety and processing technology of the tea. According to different processing techniques, tea can be divided into six categories with the increase in the degree of tea fermentation: green tea, white tea, yellow tea, oolong tea, black tea and dark tea. The initial processing stage of green tea involves steaming or roasting, which subsequently inactivates polyphenol oxidase to prevent oxidation. Therefore, green tea retains the natural structure and chemical composition of its polyphenolic compounds,

and therefore the content of TPP, L-TH and caffeine in green tea is higher than other teas. After picking of tea leaves, lightly fermented white tea is usually withered rather than steamed, leaving the oxidative enzymes in the tea not being inactivated, which leads to the oxidization of polyphenols and ultimately decrease in the polyphenol content (Chen, Shi, et al. 2020). The lowest polyphenol content of white tea may be equivalent to half the level of green tea (Ning et al. 2016; Zhao et al. 2019; Yi et al. 2015). The withering process may also lead to lower L-TH and caffeine content of white tea (Chen, Shi, et al. 2020; Hilal and Engelhardt 2007). The content of TPP is negatively correlated with the degree of tea fermentation (Gao, Huang, and Li 2016; Zhang et al. 2018; Zhao et al. 2019). Zhao et al. (2019) reported the TPP content in different tea leaves: green tea > yellow tea > oolong tea > dark tea > black tea > white tea. In terms of caffeine, green tea, dark tea and yellow tea have more and roughly equal content, followed by black tea and white tea, and oolong tea has the lowest caffeine content (Yi et al. 2015). Moreover, green tea, yellow tea, and oolong tea have similar L-TH content, followed by black tea and white tea, and dark tea has the lowest L-TH content, which is less than half that of green tea (Jiang et al. 2019). Nevertheless, although fermented teas have lower levels of TPP, L-TH and caffeine than green tea, they are generally higher in tea pigments and tea saponins (Wong, Sirisena, and Ng 2022). Zhao et al. (2019) compared the antioxidant properties of different types of tea: green tea > yellow tea > oolong tea > black tea > dark tea > white tea. The variation in the content of different active ingredients in tea may be the main reason for some confusing results of different epidemiological experiments on the improvement of cognitive function of tea drinking (Tomata et al. 2016; Feng et al. 2008).

Over the past decade, numerous studies have demonstrated the neuroprotective properties of tea. Compared with conventional drugs, the neuroprotective effect of tea has shown the advantages of multiple targets, nontoxicity and good synergy. The effects of TPP, L-TH and caffeine in tea on nerve function have attracted extensive attention. This paper reviews past studies on the action of tea and its active ingredients in AD, briefly outlines the mechanisms of action of individual tea active substance separately, and summarizes the potential mechanisms of modulating AD from a target point of view. Furthermore, this review presents the remaining problems and shortcomings of current research to provide a basis for future studies.

Pathological mechanism of AD

The neuropathological hallmarks of AD are the formation of extracellular amyloids and intraneuronal neurofibrillary tangles (NFTs) induced by hyperphosphorylation of Aβ peptide and microtubule-associated tau protein as well as selective large-scale hippocampal neuronal loss (Murphy and Levine 2010; Goncalves, Sodero, and Cordeiro 2021). The main pathogenesis of AD has been summarized and depicted in Figure 2 (Luo et al. 2021; Anand et al. 2017).
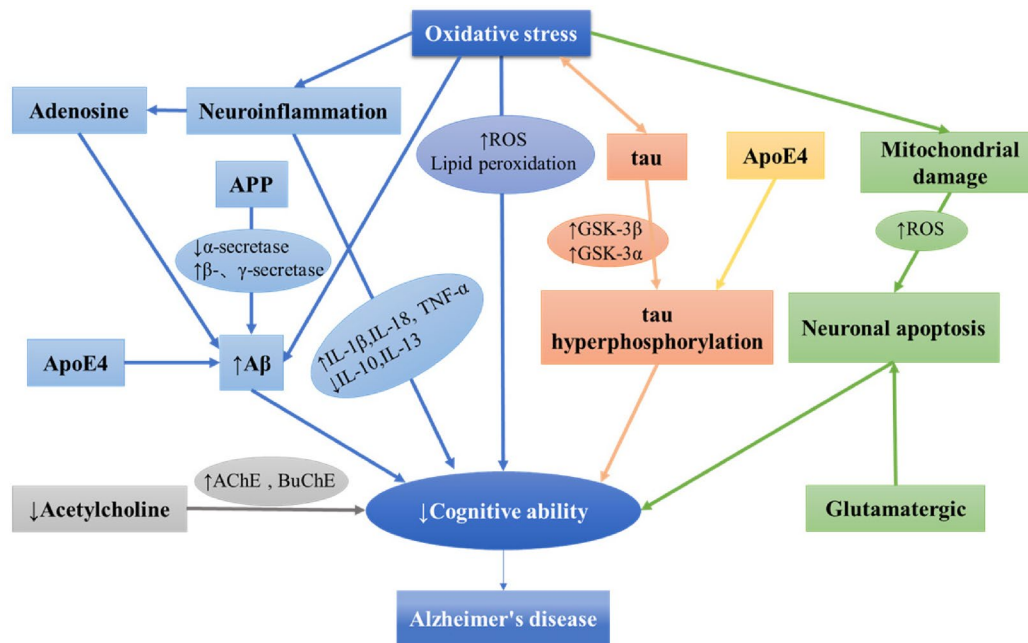
Figure 2. Possible pathogenesis of AD.

Aβ theory

As the triggering event and the most important factor, the Aβ theory is related to the imbalance between the production of Aβ by β-secretase (BACE1) and γ-secretase through proteolysis of amyloid precursor protein (APP) and the clearance of the produced Aβ (Murphy and Levine 2010). The newly Aβ generated forms a dynamic equilibrium between soluble $Aβ_{1-40}$ and deposited $Aβ_{1-42}$ (Rajendran et al. 2013). Soluble $Aβ_{1-40}$ can be cleared out of the brain and enter the plasma with a concentration gradient, while the deposited toxic $Aβ_{1-42}$ is difficult to clear due to its strong hydrophobicity. This phenomenon makes Aβ prone to aggregation, which leads to the deposition of amyloid neuritis plaques, thus disrupting cell function and ultimately leading to AD.

Tau protein theory

The Aβ theory cannot fully explain the pathogenesis of AD. Tau is a highly soluble protein whose biological activity is associated with microtubules dependent on the degree of phosphorylation (Iqbal et al. 2010). Hyperphosphorylated tau uncoupled from microtubules can aggregate into tangles and inhibit microtubule trafficking (Anand et al. 2017), eventually leading to dysregulation of the neuronal system and axonal damage (Du, Wang, et al. 2018). The changes in Aβ oligomers and tau protein have been reported as the most crucial factors in neuronal dysfunction in AD pathology (Stoothoff and Johnson 2005; Strooper 2010).

Oxidative stress theory

AD is closely related to cellular oxidative stress (Browne and Beal 1994), which is associated with the accumulation of reactive oxygen species (ROS) in the brain due to the imbalance between ROS generation and the scavenging activity of antioxidants (Huang, Zhang, and Chen 2016). ROS can respond rapidly to the easily oxidized lipids in the brain, further leading to brain dysfunction (Huang, Zhang, and Chen 2016). In addition, ROS may disrupt the functions of mitochondrial antioxidant enzymes (SOD1 and SOD2), thereby impairing the mitochondrial electron transport system and elevating ROS levels, which ultimately activates caspases and leads to neuronal apoptosis (Moreira et al. 2010). Furthermore, oxidative stress can increase the production and aggregation of Aβ, which promotes tau hyperphosphorylation and the formation of ROS (Makhaeva et al. 2015).

Neuroinflammation

Neuroinflammation is considered to be an important mechanism that leads to the progression of neurodegenerative diseases (Luo et al. 2021). As the innate immune cells of the central nervous system, microglia produce a series of toxic factors to neurons, including interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), nitric oxide (NO) and superoxide (Block and Hong 2005). Microglia activation is thought to play a key role in selective neuronal damage, which exhibits important pathological implications in AD (Li et al. 2004).

ApoE4

ApoE4 is considered to be the largest genetic risk for AD (Raber, Huang, and Ashford 2004), which advances the age of AD onset and increases the risk in a gene dose-dependent manner. ApoE4 promotes the accumulation, aggregation and

deposition of Aβ in the brain. Since ApoE4 has a lower affinity for Aβ than other ApoE isoforms (ApoE2, ApoE3), ApoE4 may be less efficient to clear Aβ within the blood-brain barrier (BBB). In addition, ApoE4 also induces abnormal brain cholesterol metabolism, further increasing Aβ production and promoting AD risk. ApoE is mainly produced by astrocytes, which makes up 40% of all brain cells. It transports lipoprotein-bound cholesterol from circulating plasma to the brain, regulated by the BBB. ApoE4 is less efficient in transporting cholesterol from astrocytes to neurons with a low binding capacity to plasma cholesterol. Therefore, high ApoE4 levels may elevate the levels of cholesterol in plasma and astrocyte (Zhou and Zhang 2021).

Adenosine theory

Adenosine is an endogenous neuroprotective agent abundantly present in the central nervous system, and its extracellular concentration increases with brain injury, neuroinflammation, and aging (Dias et al. 2013). The effects of adenosine are mediated through interactions with G protein-coupled receptors called adenosine receptors, such as the inhibitor adenosine receptor A1 (A_1R) and the agonist adenosine receptor A2A ($A_{2A}R$) (Moro et al. 2003). Aging leads to an imbalance in the expression of A_1R and $A_{2A}R$, further causing cognitive impairment and increased risk of AD (Cunha et al. 1996; Almeida et al. 2003). Furthermore, the activation of $A_{2A}R$ increases their coupling to G proteins and elevates the level of adenylate cyclase (AC), further leading to the conversion of adenosine monophosphate (AMP) to cyclic adenosine monophosphate (cAMP) and higher levels of protein kinase A (PKA). Calcium channels are more phosphorylated and lead to overload of intracellular calcium (Dias et al. 2013), which stimulates the production of Aβ and tau proteins as well as increases oxidative stress and neuroinflammation, ultimately elevating the risk of AD.

Cholinergic hypothesis

The cholinergic hypothesis states that AD begins with a deficiency of acetylcholine (AChE), and cholinesterase inhibitors play an important role in the treatment of AD. AD can decrease the neurotransmitter levels and reduced AChE content exerts a crucial role in AD pathogenesis (Anand et al. 2017). Cholinergic system dysfunction is associated with the formation of NFTs and the resulting degeneration of the basal ganglia of Meynert cholinergic neurons (Fine et al. 1997). The presence of NFTs and Aβ plaques leads to loss of cholinergic synapses.

Glutamatergic hypothesis

Glutamate is an excitatory neurotransmitter that acts on N-methyl-D-aspartic acid (NMDA) receptors and plays a key role in learning and memory. The flow of calcium ions into neurons activates various types of enzymes and produces ROS (Kakuda 2011). This continuous reaction is thought to lead to neuronal cell death. Soluble Aβ oligomers increase glutamate in the synaptic gap and may induce excitotoxicity. In this pathological state, increased ROS production and mitochondrial fragmentation have been observed in different models (Ide et al. 2018). Therefore, the glutamatergic system has also been suggested as a target for AD therapy.

Mitochondrial cascade hypothesis

The mitochondrial cascade hypothesis offers unique AD perspectives, which proposes that alterations in mitochondrial function regulate Aβ homeostasis. Swerdlow, Burns, and Khan (2014) proposed the mitochondrial cascade hypothesis that individuals start with a specific level of mitochondrial function, which declines at a specific rate individually (Swerdlow and Khan 2004; Swerdlow, Burns, and Khan 2014). Ultimately, mitochondria decline beyond a threshold to induce AD-related histological changes. In familial AD, if changes in APP, α secretase form of soluble APP (sAPPα), or Aβ homeostasis induce mitochondrial dysfunction, these changes may eventually activate pathways related to late-onset AD.

The relationship between diet and AD

With no cure or preventive treatment for AD, there is an urgent need to find ways to prevent and delay the onset or reverse the disease process. Available evidence shows that there is a correlation between healthy eating compliance and AD incidence and prevalence (Figure 3). A systematic review found that 50 out of 64 studies revealed a significant association between diet and AD incidence (Yusufov, Weyandt, and Piryatinsky 2017). AD may be caused by defects in the supply chain of cholesterol, fat and antioxidants. A diet with high glycemic index, high content of carbohydrates (especially fructose) and relatively low content of fat and cholesterol will lead to the damage of astrocytes, which will be accelerated by the excessive energy demand related to the increase of cholesterol synthesis due to the lack of sufficient blood supply. Once astrocytes can no longer provide enough cholesterol, fat and antioxidants, neurons also begin to be damaged (Seneff, Wainwright, and Mascitelli 2011). Epidemiological findings consistently indicate a high degree of compliance with dietary patterns, characterized by high intake of fruits, vegetables, grains and beans, as well as low meat, high-fat dairy products and candy, which are always associated with a lower risk of AD (Hill et al. 2019).

Clinical and epidemiological evidence suggests that lifestyle factors, especially nutrition, may be the key to the control of AD (Pasinetti and Eberstein 2008). The composition of macronutrients and micronutrients divides the diet into Western-style diet (food containing a large amount of animal protein, saturated fat, salt and sugar), Mediterranean diet (diet containing protein and fat from plants, some lean protein and high monounsaturated fatty acid content), ketogenic diet (low carbohydrate and high fat), high-sugar diet and high-fat diet (low protein, high saturation,
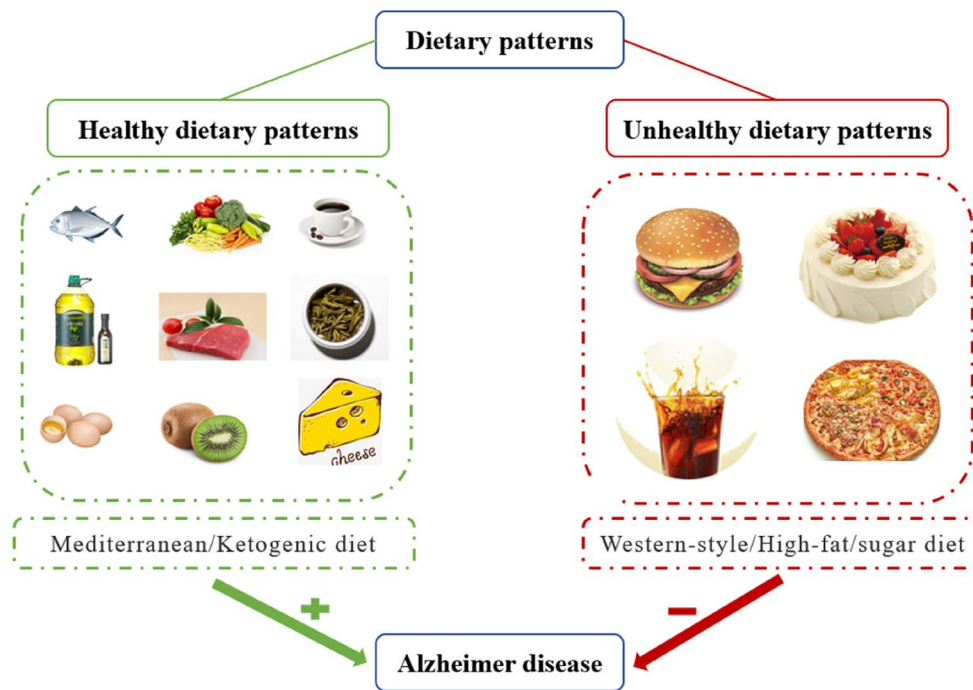
Figure 3. The relationship between diet pattern and AD.

monounsaturated polyunsaturated fat level and high cholesterol level) (Wood and Sullivan 2022). The prevalence of AD in Japan is related to the long-term nutritional transition from the traditional Japanese diet to the Western diet, in which the AD rate increased from 1% in 1985 to 7% in 2008 (Grant 2014). Moreover, another study suggests that Western-style diet can trigger AD by accelerating inflammation (Więckowska-Gacek et al. 2021). A low carbohydrate, high-fat ketogenic diet may help reduce the damage associated with these pathologies, because the ketogenic diet can reduce the impact of impaired glucose metabolism by providing ketones as a supplementary energy source. In addition, this diet may help to reduce the accumulation of amyloid plaques and reverse Aβ toxicity (Broom, Shaw, and Rucklidge 2019). Mediterranean diet compliance reduces the risk of AD, and may help maintain intestinal symbiosis (Solch et al. 2022). A high-fat diet can exacerbate memory impairment (Rollins et al. 2019). Another study showed that a high sugar diet during pregnancy promoted the AD phenotype (Di Meco et al. 2018). Nevertheless, it is worth noting that the intake of high fat, high sugar and high cholesterol does not affect the pathogenesis of tau in the mouse model of Alzheimer's disease (Chu et al. 2022). Therefore, current evidence demonstrates that Mediterranean style dietary patterns and ketogenic diets are associated with a decrease in AD biomarkers and subsequent pathology. On the contrary, the hyperglycemia and high saturated fat diet can increase relevant AD biomarkers.

Tea and AD

Tea is the most popular plant beverage rich in antioxidants (Graham 1992). The tea leaves are picked, dried and steamed to prevent the activation of polyphenol oxidase and preserve the nutritional value of tea leaves (Graham 1992). Tea has exhibited significant antioxidant, anti-inflammatory, antibacterial, anticancer, antihypertensive, neuroprotective and cholesterol lowering properties (Hayat et al. 2015). Drinking tea can modulate the diversity of the gut microbiota to improve the gut microecosystem (Bond and Derbyshire 2019). A cross-sectional survey of elderly Chinese found that the standardized prevalence of AD was 6.9%, and tea drinking was associated with a lower prevalence of AD and cognitive impairment (Yang, Jin, et al. 2016). Similarly, a community study in Singapore reported that the participants with a tea drinking habit were associated with better cognitive functions (Feng et al. 2010). In another study, the prevalence of cognitive impairment was lower with drinking green tea (Gu et al. 2018). Contrastly, several studies have not shown any benefit from green tea for AD (Ma et al. 2016). It was reported that drinking black tea was associated with better cognitive performance, while drinking green tea was not (Shen et al. 2015). Few studies have been conducted on oolong and other teas. Feng et al. (2008) reported an inverse correlation between oolong tea consumption and the presence of cognitive impairment, but Tomata et al. (2016) demonstrated no significant association between oolong tea and dementia. Overall, there is growing epidemiological evidence to support the effectiveness of tea consumption on cognitive impairment, which may ameliorate dementia and cognitive decline. While some studies have shown no significant association between tea drinking and cognitive improvement, short follow-up periods, small sample sizes and insufficient levels of functional components in some teas, such as low levels of tea polyphenols in the more fermented black teas, should be accounted for these inconsistent results. Besides, a typical cup of green tea, with 2.5 g of tea leaves brewed for 3 min in 250 ml hot water,

usually contains 620–880 mg of water-extractable materials, of which about a third are catechins. EGCG accounts for 50–75% of the total catechins. Thus, a freshly brewed cup of green tea may contain 130–180 mg of EGCG, 37.5 mg caffeine and 40 mg L-TH.(Yang and Pan 2012; Scheid et al. 2012; Bond and Derbyshire 2019). A meta-analysis of 17 studies showed that for 100 mL/d, 300 mL/d, and 500 mL/d increase in tea consumption, the risk of AD was reduced by 6%, 19%, and 29%, respectively (Liu et al. 2017). Considering the tea drinking habits in different regions, two cups of green tea or three cups of black tea per day may be appropriate for preventing AD (Table 1).

Tea active compounds and AD

Tea contains many bioactive compounds, such as TPP, caffeine, L-TH, GABA and PQQ, which contribute to its neuroprotective effects. Potential neuroprotective mechanisms include the regulation of signal pathways, which can not only regulate the hydrolysis of APP to control the production of Aβ, but also play the role of antioxidant and anti-inflammatory through its mediation to inhibit neuronal apoptosis and protect the nervous system. Furthermore, through the regulation of some protein kinases and neurotransmitters, it can inhibit the hyperphosphorylation and aggregation of tau and restore the cholinergic system. The potential neuroprotective mechanisms include the modulation of signaling pathways, e.g. theanine inhibits neuronal apoptosis by regulating the extracellular regulated protein kinases 1/p38 mitogen-activated protein kinase (ERK1/p38MAPK) and nuclear factor kappa-B (NF-κB) pathways, and TPP can inhibit abnormal protein production and aggregation by regulating the ERK/NF-κB pathway; alleviating the symptoms of AD through antioxidant and anti-inflammatory effects; TPP and caffeine can play a neuroprotective role by regulating neurotransmitter levels.

TPP

The structure of TPP

TPP are complexes of polyhydroxy phenolic compounds in tea leaves. TPP show various physiological activities such as antioxidant, anti-radiation, anti-aging, hypolipidemic, hypoglycemic, and antimicrobial properties. According to the main chemical components, TPP are divided into four categories: catechins, flavonoids, anthocyanins, and phenolic acids. Among them, catechins occupy the highest proportion, accounting for 60–80% of TPP. The catechins are mainly epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG). The highest content of catechins in tea leaves is EGCG, followed by ECG, and then EGC.

Catechins have a variety of phenolic groups, which makes them chemically reactive. EGCG has eight phenolic groups, all of which are potential donors of hydrogen bonds. EGCG and other catechins can bind to a variety of proteins and other biomolecules through hydrogen bonds and other interactions (Yang et al. 2009). These phenolic groups also make

catechin an effective antioxidant and scavenge free radicals (Zuo et al. 2018). In addition, catechins can chelate trace elements such as iron and copper, which can prevent the formation of reactive oxygen species. The presence of grape phenolic group also makes catechin easy to be oxidized to form quinone, which can produce oxidative stress through redox cycle. To prevent this reaction from occurring in vivo, mammalian cells have catechol-O-methyltransferase (COMT), for example, methylation of EGCG at 4'and 4″ positions to form 4″-o-methyl-(-)-EGCG and 4',4″-o-dimethyl-(-)-EGCG (Lu, Meng, and Yang 2003). This eliminates the ligno phenolic structure and prevents possible toxicity through the redox cycle.

The metabolism of TPP

It has been reported that TPP are absorbed, distributed, metabolized and excreted within 24 h. In a human study, when 1.2 g of decaffeinated green tea was ingested, the plasma level of TPP ranged from 46–268 ng/mL within 1 h after ingestion, with cumulative excretion levels of 1.6–3.2 mg within the first 24 h (Singh, Mandal, and Khan 2015). Consumption of five cups of tea per day increases the concentration of TPP in plasma by a factor of 12, which is sufficient to exert antioxidant activity (Sharma et al. 2007). This data is further supported by animal studies, where administration of 35 mg/kg/d of green TPP not only prevented oxidative damage and memory regression, but also delayed aging (Singh, Mandal, and Khan 2015). Oral catechins are usually excreted from the body within 4–6 hours, and ingestion of catechins every 4–5 h is necessary unless sustained release can be guaranteed (Janle et al. 2008). TPP is mainly absorbed in the small intestine (about 10–20%) (Spencer et al. 2001), and metabolized in intestinal cells, liver and other organs through methylation, glucuronidation and sulfation (Chen and Yang 2020). Unabsorbed TPP entering the colon is degraded by the microbiota. Some metabolites are also absorbed throughout the body and excreted in the urine, while those that are not absorbed are excreted in the feces (Roowi et al. 2010).

Effects of TPP on AD

As the main bioactive compound of green tea, EGCG has a well-documented potential to treat neurodegenerative diseases. It has been reported that EGCG can interact with misfolded proteins, such as Aβ, tau, etc., which contribute to the pathogenesis of AD (Goncalves, Sodero, and Cordeiro 2021).

EGCG can reduce $Aβ_{1-42}$-induced memory dysfunction by enhancing α-secretase, while inhibiting β- and γ-secretase by suppressing the ERK/NF-κB pathway (Lee et al. 2009). In addition, EGCG also prevented $Aβ_{1-42}$-induced apoptosis. Lee et al. found that in an LPS-induced AD model, EGCG prevented astrocyte activation and elevation of pro-inflammatory cytokines, including TNF-α, and increased inflammatory proteins, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Lee et al. 2013). In a streptozotocin-induced AD model, EGCG could reverse oxidative stress and decrease acetylcholinesterase

Table 1. Association between tea consumption and cognitive disorders.

Types of tea	Intake	Number of subjects	Main results	Ref.
Green tea	≥2 cups/d	1,003	Higher consumption of green tea is associated with lower prevalence of cognitive impairment in humans Odds ratio (OR): 0.46 (95%CI: 0.30, 0.72), Compared with the reference (≤3 cups/wk)	(Kuriyama et al. 2006)
Black and green tea	<2 cups/d 2–4 cups/d ≥4 cups/d	9,375	Black tea consumption is associated with better cognitive ability in the elderly OR: 0.77 (95%CI: 0.56, 1.07), OR: 0.62 (95%CI: 0.47, 0.81), OR: 0.49 (95%CI: 0.36, 0.66), Compared to not consuming. Green tea intake did not affect the OR for cognitive impairment significantly	(Shen et al. 2015)
Green tea	>1 cup/d	13,988	Green tea consumption is significantly associated with a lower risk of event dysfunction	(Tomata et al. 2012)
Green tea	>1 time/wk	4,674	Habitual tea consumption, especially high-frequency and green tea consumption, was significantly associated with a lower prevalence of cognitive impairment in middle-aged and older individuals	(J. Zhang et al. 2020)
Black, oolong and green tea	≥1–2 cups/d	716	Both black/oolong tea and green tea consumption were associated with better cognitive performance. The protective effect of tea consumption on cognitive function is not limited to specific types of tea.	(Feng et al. 2010)
Black and green tea	Low, medium and high levels of tea intake	2,501	It reported an inverse association of green tea drinking with cognitive impairment. We found an inverse association of black or oolong tea drinking with both cognitive impairment and cognitive decline. Although our cross-sectional analysis supported an association of green tea with less cognitive impairment, this association cannot be meaningfully separated from that due to black or oolong tea, given the small numbers of those who drank green tea only.	(Feng et al. 2008)
Green tea	<1 time/d	2,622	Higher green tea intake was not significantly associated with AD or memory loss	(Fischer et al. 2018)
Green tea	1–7 times/wk	1,143	An increase of green tea intake significantly lowered the OR for cognitive impairment	(Kitamura et al. 2016)
Green tea	≥3 cups/wk	2,131	Green tea consumption reduced the risk of mild cognitive impairment in male participants (OR = 0.657, p= 0.019). Neither black tea nor oolong tea was found to be associated with a reduced risk of developing mild cognitive impairment	(Xu et al. 2018)
Green tea	7 times/wk 1–6 times/wk	723	Green tea consumption is significantly associated with the risk of cognitive decline OR: 0.32 (95%CI: 0.16, 0.64), OR: 0.47 (95%CI: 0.25, 0.86).	(Noguchi-Shinohara et al. 2014)
Green and black tea	1–6 cups/d	377,592	Moderate consumption (1–6 cups/day) of tea exerts a significant protective effect. Within 3 cups/d, the HR for dementia was 0.943 (95% CI: 0.907–0.981) per cup increase, indicating an approximately 6% reduced risk for one extra cup a day.	(Hu et al. 2022)
Green, black and oolong tea	>1 cup/d	13,645	More frequent green tea consumption was associated with a lower risk of incident dementia (hazard ratio for ≥5 cups/d versus <1 cup/d: HR: 0.73; 95% confidence interval: 0.61–0.87). Non-significant association between oolong and black teas and dementia	(Tomata et al. 2016)

Table 2. Effects and mechanisms of TPP on Alzheimer's disease.

Component	Model	Does	Effects	Mechanisms	Ref.
EGCG	AD transgenic mice	2mg/kg or 6mg/kg EGCG 4wk	Significantly reduce Aβ and the injury of hippocampal neurons	Reduce the expression of Aβ	(He et al. 2012)
EGCG	APP Tg CRND8AD mice	50mg/kg/d, 4 months	It has beneficial effects on cognition and significantly reduces the level of soluble Aβ$_{1-42}$ in cortex and hippocampus	Reduce the expression of Aβ	(Walker et al. 2015)
EGCG	APPsw mice	EGCG (20mg/kg) intraperitoneal injection and EGCG (50mg/kg) oral	Reduce the deposition of Aβ and inhibit p-tau	Reduce Aβ deposition and inhibit the phosphorylation level of tau	(Rezai-Zadeh et al. 2008)
EGCG	Exposure to Aβ Hippocampal neurons	EGCG and exposure to Aβ joint processing	It can improve the cell survival rate and reduce the activities of malondialdehyde and caspase, which has a protective effect on Aβ-induced neuronal apoptosis	Anti-oxidation	(Choi et al. 2001)
EGCG	APP/PS1 mice	2mg/kg/d, 4 wk	Prevent the toxicity induced by Aβ$_{1-42}$, improve cell viability, inhibit the apoptosis of mouse cortical neurons, reduce the abnormal ultrastructural swelling of ER, and down regulate the expression of ER stress-related proteins.	Inhibit neuronal apoptosis	(Du, Liu, et al. 2018)
EGCG	AD transgenic mice	Oral, 15mg/kg	It decreases the levels of Aβ$_{1-42}$ and BACE1 in frontal cortex and hippocampus and prevent the hyperphosphorylation of tau	Reduce Aβ and tau hyperphosphorylation	(Guo, Noble, et al. 2017)
Catechin/ Polyphenol E	Aged rats	Take (+)—catechin or polyphenol E	It shows significant improvements in visuospatial work and episodic memory. Age related neuroinflammation is also alleviated by increasing the expression of sirtuin-1 in the hippocampus	Antioxidation and anti-inflammation	(Ramis et al. 2020)
Catechin	Aβ25-35-induced model	50 mg/mL	Reduce apoptosis and caspase-3 activity, so as to reduce neuronal death. Lipid peroxidation and protein oxidation were weakened.	Anti-oxidation	(Suganthy and Devi 2016)
EGCG	SAMP8	5 and 15 mg/kg,8 wk	It showed competitive inhibition on ache and BuChE	Cholinesterase inhibition	(Okello and Mather 2020)
Catechin	AD patients	After taking the medicine for 2 months, simple mental state examination (MMSE) was carried out, 2 g / d each time, taking the medicine twice.	The total antioxidant capacity and MMSE score increased significantly, and the contents of 8-OHdG, malondialdehyde and carbonyl decreased.		(Carmichael et al. 2018)
EGCG	Rat cortical astrocytes	2μg/ml EGCG for 48h. The supernatant was then treated with Aβ1-40 under extracellular conditions for 12h	It causes increased expression of brain caffein, resulting in Aβ$_{1-40}$ degradation by activating ERK and PI3K pathways	Facilitate degradation of Aβ	(Yamamoto et al. 2017)
EGCG	Al-induced AD model	100mg/kg AlCl3, oral, 60 d, then 10mg/kg EGCG and EGCG loaded nanoparticles, 30d	Reduce neurobehavioral defects and Aβ and Tau pathology	Reduce Aβ and tau, inhibition of cholinesterase activity. Anti-oxidation	(Singh et al. 2018)
ECG	APP/PS1 mice	100mg/ kg,2 months	Reduce Aβ plaque in the brain	Reduce the Aβ plaques	(Chen, Shi, et al. 2020)

Table 3. Effects and mechanisms of caffeine on Alzheimer's disease.

Component	Model	Does	Effects	Mechanisms	Ref.
Caffeine	APPsw (K670N/ M671L) male and female mice	0.3 g/L, 5.5 months;	Reduce the level of Aβ in hippocampus and restore brain adenosine level	Reduce the level of Aβ	(Arendash et al. 2006)
	APPsw (K670N/ M671L) mice	2*1.5 mg/d,2 wk	Promote brain function and exert neuroprotective and anti apoptotic effects	Reduce the level of Aβ and inhibit neuronal apoptosis	(Zeitlin et al. 2011)
	APPsw (K670N/ M671L) mice	0.6 mg/d, 1 month	Prevention of cognitive impairment	Anti-oxidation	(Dragicevic et al. 2012)
	APPsw (K670N/M671L) and Indiana (V717F) mutation male mice	0.0395% crude caffeine /0.0375% pure caffeine, 2 months;	Partially prevent memory deficits (crude caffeine works better). Crude caffeine can reduce Aβ$_{1-42}$ level, inhibition Aβ and reduce the number of Aβ plaques in the hippocampus. Both can stop Aβ Induced neuronal cell death and inhibited caspase-3 activity. Crude caffeine also has antioxidant and anti-inflammatory effects in APPsw mice.	Reduce the level of Aβ. Antioxidation and anti-inflammation	(Chu et al. 2012)
	APPsw and APPsw/PS1 mice	1.5 mg	Long-term caffeine intake improved cognitive functions in APPsw and APPsw/PS1 mice. Decreased Aβ levels in the plasma were observed after single administration of caffeine and long-term caffeine treatments in both transgenic mice models. Chronic caffeine treatment reduced soluble Aβ level in the cortex and hippocampus and insoluble Aβ level in the hippocampus in APPsw mice. Acute caffeine administration rapidly reduced the Aβ level also in the interstitial fluid in the hippocampus but did not affect Aβ elimination in APPsw mice.	Anti-inflammation. Reduce the generation of Aβ	(Cao et al. 2009)
	APPsw and APPsw/PS1 mice		Increase the levels of G-CSF, IL-6 and IL-10 in plasma and improve cognitive level	Reduce the level/ deposition of Aβ, anti-inflammation	(Cao et al. 2011)
	APPs and APPsw/PS1 mice	0.75 mg/d or 1.5 mg/d 8 wk	Improved spatial learning ability and memory ability	Reduce the level of Aβ	(Han et al. 2013)
	THY-Tau22 male mice	0.3 g/L, 10 months	Prevent spatial memory defects and improve memory performance	Inhibit the phosphorylation level of tau	(Laurent et al. 2014)
	THY-Tau22 female mice	0.3 g/L	Exposure to caffeine during pregnancy can lead to accelerated physiological and cognitive impairment		(Zappettini et al. 2019)

Table 4. Effects and mechanisms of L-TH on Alzheimer's disease.

Component	Model	Does	Effects	Mechanisms	Ref.
L-TH	Cd-induced mice	100 or 200 mg/kg/d	L-TH protects mice against Cd-induced neurotoxicity through reducing brain Cd level and relieved oxidative damage and tau hyperphosphorylation	Anti-oxidation and relieve tau hyperphosphorylation	(Ben et al. 2016)
	APP/PS1 mice	0.1 mg/mL and 0.4 mg/mL, 15 d	Improve the memory and long-term enhancement of hippocampus in AD mice	Repairing dopamine dysfunction for neuroprotection	(Zhu et al. 2018)
	Aβ-induced mice	2, 4 mg/kg, 5 wk	Signifcantly weakened Aβ$_{1-42}$ induced memory impairment, reduced Aβ$_{1-42}$ level and accompanying Aβ$_{1-42}$ induced neuronal cell death in cerebral cortex and hippocampus	Inhibits neuronal apoptosis and reduce the level of Aβ. Antioxidant	(Kim et al. 2009)
	APPsw tg SH-SY5Y		It significantly attenuated the apoptosis induced by L-glutamate. Meanwhile, the activation of c-Jun N-terminal kinase and caspase-3 induced by L-glutamate was inhibited by L-TH.	Inhibit NMDA-related pathways and neuronal apoptosis. Anti-inflammation	(Di et al. 2010)
	Thick synaptosomes male Weasels		Inhibition of glutamate transport in rat brain neurons and astrocytes	Inhibit glutamate transport for neuroprotection	(Kakuda et al. 2008)
	SH-SY5Y		Prevent oxidative damage to neurons	Anti-oxidation	(Jo et al. 2011)
	AD rat	0.1–1 μg/mL	Reduce expression of inflammation related factor TNF-α and IL-1β	Anti-inflammation	(Park et al. 2018)

TABLE 5. Effects of different teas or tea active ingredients on intestinal microbiota.

Test Object	Model	Does	Results	Ref.
EGCG, GCG and epigallocatechin-3-O-(3″-O-methyl)-gallate (EGCG3″Me)	Healthy people	Fermentation was initiated by adding 150 µL of fecal slurry to 1350 µL of culture medium containing EGCG, GCG, EGCG3″Me or FOS (positive control)	EGCG, GCG and EGCG3″Me promoted the growth of *Bifidobacterium* spp. and *Lactobacillus/Enterococcus* groups and exhibited inhibitory effects on the growth of *Bacteroides–Prevotella*, *Clostridium histolyticum* and *Eubacterium–Clostridium* groups, while they did not affect the population of total bacteria.	(Zhang et al. 2013)
Pu-erh tea extract	Specific pathogen-free (SPF) BALB/c female mice	1.0, 2.0, and 3.0 g/kg-bw per day	Feeding pu-erh tea extract helped mice regain weight and alleviate intestinal inflammation. Further assessment of intestinal flora revealed that pu-erh tea extract promoted the growth of intestinal probiotics and inhibited pathogenic bacteria.	(Zhang et al. 2021)
Fu brick tea polyphenols	High fat diet (HFD)-fed rats	100 mg/kg/day, 12 wk	FBTP supplementation improved the intestinal oxidative stress and intestinal barrier function, including intestinal inflammation and the integrity of the intestinal barrier	(Zhou et al. 2021)
Black tea	Sprague–Dawley (SD) rats	Rats were administered black tea powder (suspended in distilled water) via intragastric gavage at 1.5 g/kg body weight per day, 4 wk	It increased α-diversity and modulated β-diversity of the gut microbiota. Additionally, black tea enriched several short-chain fatty acid (SCFA) producers but suppressed genus *Lactobacillus*.	(Gao, Xu, and Yin 2020)
Duyun Compound Green Tea	HFD-induced mice	90/210/840 mg/kg per day, 28 d	The compounds in tea may be able to attenuate imbalances of intestinal microbiota induced by poor diet, acting as a therapeutic agent in obesity or other diseases associated with gut dysbiosis	(Zhou et al. 2021)
TPP from green, black and oolong tea	Healthy people	Fermentation was initiated by adding 150 µL of fecal slurry to 1350 µL of culture medium containing TPP or FOS (positive control)	TPP can modulate the intestinal flora and generate SCFA, and contribute to the improvements of human health.	(Sun et al. 2018)
TPP	SD rats	200 mg/kg, 8 wk	TPP significantly decreased the levels of TNF-α, IL-6 and malondialdehyde	(Xia et al. 2019)
Caffeine	Healthy people	High (≥82.9 mg) vs. low (<82.9 mg) consumption of caffeine	Higher caffeine consumption was associated with increased richness and evenness of the mucosa-associated gut microbiota, and higher relative abundance of anti-inflammatory bacteria, such as Faecalibacterium and Roseburia and lower levels of harmful Erysipelatoclostridium.	(Gurwara et al. 2019)
TPP	Male canines	Low (0.48% g/kg), medium (0.96% g/kg), or high (1.92% g/kg), 18 wk	TPP decreased the relative abundance of *Bacteroidetes* and *Fusobacteria* and increased the relative abundance of *Firmicutes*. The relative proportion of *Acidaminococcus*, *Anaerobiospirillum*, *Anaerovibrio*, *Bacteroides*, *Blautia*, *Catenibacterium*, *Citrobacter*, *Clostridium*, *Collinsella*, and *Escherichia*. TPP decreased expression levels of inflammatory cytokines, including TNF-α, IL-6, and IL-1β, and inhibited induction of the TLR4 signaling pathway.	(Li et al. 2020)
Fuzhuan Brick Tea Polysaccharide	C57BL/6 mice	100, 200, and 400 mg/kg-bw, 37 d	It alleviated inflammation and disruption of the intestinal microbiota, promoted the proliferation of beneficial microbiota such as *Lactobacillus* and *Ackermannia*, and significantly increased the levels of short-chain fatty acids.	(Yang, Ren, et al. 2021)
Green and dark tea extract	C57BL/6 female mice	5 mg/kg bodyweight/day, 4 wk	It improved inflammation and gut microbiota ecological dysregulation and downregulated TLR4/MyD88/NF-κB pathway	(Liu et al. 2020)
Tea water extracts	C57BL/6J HFD mice	1% water extracts of green tea, oolong tea and black tea, 28 wk	Tea extracts changed the overall composition of gut microbiota and decreased the relative abundance of family *Rikenellaceae* and *Desulfovibrionaceae*.	(Liu et al. 2019)

activity, thus exerting neuroprotective effects (Biasibetti et al. 2013). In another study, after oral administration of EGCG (50 mg/kg) in TG APPsw transgenic rats, the content of soluble phosphorylated tau protein in brain was decreased, and the content of insoluble phosphorylated Tau protein was increased, and the content of both was close to normal levels (Rezai-Zadeh et al. 2008). The phenomenon indicated that EGCG can improve the pathological phenomenon of Tau protein. Specifically, EGCG can activate nuclear factor-erythroid2 related factor 2 (NRF2) in SH-SY5Y neuroblastoma cells, induce autophagy, and increase the mRNA levels of adaptor proteins NDP52 and p62 to mediate neuroprotection. In a transgenic AD mouse model expressing multiple APP mutations, oral administration of EGCG (50 mg/kg/d) for 4 months showed a beneficial effect on cognition and reduced the level of soluble $A\beta_{1-42}$ in cortex and hippocampus (He et al. 2012). Similarly, both intraperitoneal injection of EGCG (20 mg/kg) and oral administration of EGCG (50 mg/kg) inhibited the p-tau subtype, suggesting that EGCG downregulates the expression of tau protein (Rezai-Zadeh et al. 2008). Using $A\beta_{1-42}$-induced SH-SY5Y cells and APP/PS1 transgenic mice, Du, Liu, et al. (2018) found that EGCG prevented $A\beta_{1-42}$-induced toxicity, increased cell viability, and inhibited APP/PS1 transgene apoptosis of cortical neurons. Meanwhile, EGCG could attenuate abnormal ultrastructural swelling of the endoplasmic reticulum (ER) and down-regulated the expression of ER stress-related proteins. These results suggest that EGCG may alleviate the neurotoxicity of AD by inhibiting ER stress-related neuronal apoptosis. $A\beta_{1-42}$ reduced the protein and gene expression levels of peroxisome proliferator activated receptor-γ coactivator-1α (PGC-1α) in neuroblastoma N2a cells (Yuqin Zhang et al. 2017). The overexpression of PGC-1α can attenuate $A\beta_{1-42}$-induced cell death and caspase-3 activation, and reduce pro-inflammatory cells by inhibiting the transport of nuclear factor NF-κB p65 from the cytoplasm to the nucleus and $A\beta_{1-42}$-induced Iα degradation factor levels (Zhang et al. 2017). Long-term oral administration of EGCG (15 mg/kg) improved the memory function of AD transgenic mice in the Y-maze and Morris water maze tests. In addition, EGCG decreased the levels of $A\beta_{1-42}$ and β-secretase in the frontal cortex and hippocampus and prevented the hyperphosphorylation of tau (Guo, Noble, et al. 2017). In an experiment using human SH-SY5Y neuroblastoma and rat pheochromocytoma (PC12) cells, EGCG promoted α-secretase-mediated release of non-amyloidogenic sAPPα into the culture medium (Levites et al. 2003). Inhibition or downregulation of PKC blocks EGCG-induced secretion of sAPPα by inducing the phosphorylation of PKC. EGCG also protects PC12 cells from Aβ toxicity. Up-regulation of enkephalinase expression can also reduce Aβ levels to alleviate AD symptoms (Chang et al. 2015).

As the most widely and deeply studied substance in green tea, the regulatory mechanism of EGCG on AD can be summarized as follows: EGCG can remove misfolded proteins (Aβ and tau) and reduce their expression and aggregation by regulating signaling pathways and activating autophagy. In addition, EGCG can eliminate ROS and reverse oxidative stress through its powerful antioxidant effect, and reduce neuroinflammation by regulating pro-inflammatory factors or inflammatory proteins such as IL-1β, TNF-α and INOS to suppress neuroinflammation. Furthermore, EGCG can protect neurology and alleviate AD by lowering acetylcholinesterase to regulate neurotransmitters, chelating metal ions to reduce neurotoxicity and blocking caspase activation.

EGC and ECG can alleviate $A\beta_{40}$ aggregation and reduce ROS generation by chelating Cu^{2+} and Zn^{2+}, thereby reducing the neurotoxicity induced by Cu^{2+}- and Zn^{2+}-$A\beta_{40}$ on neurons (Chen, Shi, et al. 2020). ECG can exert a therapeutic effect through the BBB, inhibiting the formation of senile plaques, and alleviating neuronal damage in the brains of transgenic AD mouse models (Chen, Shi, et al. 2020). Although EGCG is a potent chelating agent, it is poorly absorbed in the brain and therefore may not be as effective as ECG. Taniguchi et al. (2005) found that ECG, EC and C could inhibit heparin-induced tau protein aggregation. Inactivation of plasminogen activator inhibitor type 1 can alleviate the symptoms of AD (Luo et al. 2021). Theaflavins could inhibit plasminogen activator inhibitor 1 in a concentration-dependent manner, with an IC_{50} value of 18 μM. Theaflavins may delay the progression of AD by inhibiting the plasminogen activator inhibitor 1-dependent pathway (Skrzypczak-Jankun and Jankun 2010; Luo et al. 2021).

The safety of TPP

Meanwhile, despite the low bioavailability of TPP, higher levels of TPP show potential physiological toxicity. Feeding high doses (1%) of TPP in colitis mice caused nephrotoxic symptoms and affected liver and kidney function, resulting in oxidative damage. Similar results were observed in healthy mice. Nevertheless, when colitis mice were fed with low doses (0.01% or 0.1%) of TPP, TPP showed protective effects on organs such as liver and kidney (Murakami 2014). Therefore, the optimal dosage of TPP in the prevention and treatment of different diseases needs to be confirmed.

Caffeine

The structure of caffeine

Caffeine ($C_8H_{10}N_4O_2$) is a xanthine alkaloid extracted from tea and coffee and is present in various foods and beverages. Pure caffeine is a white powder with a strong bitter taste (Nehlig 2018). As a brain stimulant, the primary effect of caffeine is to increase brain energy metabolism, cortical activity, and extracellular acetylcholine levels, thus increasing alertness (Yenisetti and Muralidhara 2016). Different types of tea contain various amounts of caffeine varied by fermentation levels. Generally, 100 mL of unfermented green tea contained an average of 15 mg of caffeine, and semi-fermented oolong tea and fermented black tea contained an average of 17 mg of caffeine per 100 mL (Bond and Derbyshire 2019). Caffeine promotes cognitive improvement by antagonizing A_1R and $A_{2A}R$ in the brain (Fredholm et al. 1999; Londzin et al. 2021).

The metabolism of caffeine

Caffeine is rapidly and completely absorbed from the gastrointestinal tract, especially in the small intestine, with very high bioavailability (99–100%) (Arnaud 1987). Over the next 30 to 60 mins, 96.34 mg of caffeine will result in a maximum plasma concentration of 2.47 µg/mL (Arendash et al. 2006; Zhou and Zhang 2021). The hydrophobicity of caffeine allows it to quickly cross BBB, and then the caffeine concentration in the brain reaches a concentration similar to that in the blood. Therefore, oral caffeine can protect nervous system from cognitive dysfunction (Arendash et al. 2006).

Caffeine is mainly metabolized in the liver by the cytochrome P450 oxidase system, especially the CYP1A2 enzyme (Temple et al. 2017). The metabolism of caffeine is regulated by several factors, such as genetic variation, circadian rhythms, steroid hormones, pregnancy, infancy, etc. In women in particular, metabolism of caffeine is slowed during pregnancy and oral contraceptive use (Carver et al. 2014; Košir, Španinger, and Rozman 2013). In infants, early metabolism is very slow, and caffeine is metabolized at the same rate as adults until six months of age (Aranda et al. 1979).

Effects of caffeine on AD

As an adenosine analog, caffeine can non-selectively antagonize adenosine receptors to exert its pharmacological or toxicological effects. Several longitudinal studies reported that a daily intake of caffeine equivalent to 3 or more cups of coffee reduces cognitive decline in the elderly with "non-dementia" (Ritchie et al. 2007; van Gelder et al. 2007). Nevertheless, Kim, Kwak, and Myung (2015) performed a meta-analysis of 20 studies with a total of 31,479 subjects and found that caffeine intake from coffee or tea was not associated with the risk of cognitive impairment. Whereas from a large number of studies, there is increasing evidence that caffeine has an effect on cognition and the development of AD (Londzin et al. 2021). Compared with age-matched non-AD patients, AD patients consumed significantly less caffeine in the 20 years prior to being diagnosed with AD. Long-term caffeine intake may prevent aging-related memory impairment and AD (Maia and De Mendonça 2002). Similarly, AD transgenic mice given moderate caffeine intake (equivalent to 5 cups of coffee daily in humans) were prevented from developing specific cognitive impairments (Arendash et al. 2009).

The effect of caffeine on AD can be described from four aspects: (1) The hyperactive form of c-Raf-1 promotes the progression of AD by activating the NF-κB pathway and the expression of β-secretase. Caffeine can stimulate PKA activity to reduce the overactivity of c-Raf-1. (2) Caffeine can also reduce the dysregulation of GSK-3α gene, which upregulates ps1 mutation and γ-secretase expression, thereby inhibiting tau hyperphosphorylation. (3) The oxidative stress theory suggests that caffeine can inhibit the formation of ROS, while Aβ can promote the formation of ROS. ROS can damage the mitochondrial electron transport system, which in turn triggers caspases and neuronal apoptosis. (4) Caffeine can reduce high ApoE4-induced high plasma and astrocyte cholesterol levels and reduce the damage of BBB caused by hypercholesterolemia (Zhou and Zhang 2021). In addition, caffeine could also inhibit acetylcholinesterase (Pohanka and Dobes 2013) and glutamate (Gołembiowska and Dziubina 2012). In conclusion, caffeine can act on AD through the following mechanisms including reducing the phosphorylation level of Aβ and tau and eliminate the plaque and NFTs caused by their aggregation; clearing ROS and regulate inflammatory factors to reduce the level of oxidative stress and inhibit neuroinflammation; antagonizing adenosine receptor to protect neurons and competitively binding acetylcholinesterase and glutamate receptors to regulate neurotransmitters and protect nerves.

The safety of caffeine

Caffeine is safe for healthy adults, but may be detrimental for certain groups, including risks of cardiovascular function and sleep (Temple et al. 2017). Safe levels of caffeine consumption have not been determined for most children, teens, and young adults. Notably, high doses (≥200 mg/d) of caffeine consumption, caffeine consumption with cardiovascular disease or mental illness, and consumption of more than 200 mg/d caffeine during pregnancy or breastfeeding may cause adverse effects (Temple et al. 2017).

L-TH

Structure of L-TH

Theanine (TH), 5-N-ethylglutamine, with the chemical formula $C_7H_{14}N_2O_3$, is the most abundant amino acid in tea (Kojima and Yoshida 2008). It is a glutamine derivative ethylated at the N5 position with the chemical name 2-amino-4-(ethylcarbamoyl) butanoic acid, which has two chiral isomers, D- and L-Theanine (L-TH) (Mindt et al. 2020). Similar to other amino acids in nature, theanine mainly occurs in the L-(S) enantiomer form (Sharma, Joshi, and Gulati 2018). L-TH is a water-soluble compound synthesized from γ-ethylamine and L-glutamic acid (Yu and Yang 2020). L-TH has a structure similar to L-glutamine and can compete with L-glutamine for L-glutamine receptors on the surface of cell membrane. Once L-TH is taken up by cells, it is enzymatically converted to L-glutamate, increasing L-glutamate and glutathione (GSH) concentrations in tissues. Theanine can eliminate the astringency of caffeine and TPP and promote the release of tea aroma (Deng, Ogita, and Ashihara 2010; Mindt et al. 2020). L-TH has exhibited health benefits including neuroprotection (Luo et al. 2021), anti-inflammatory (Luo et al. 2021), antibacterial (Bansal et al. 2013), and regulation of lipid metabolism (Lin et al. 2020), glucose metabolism (Lin et al. 2020), and gut microbiota (He et al. 2021).

The metabolism of L-TH

In rats, the plasma concentration of L-TH reached its maximum level 0.5 h after ingestion (Unno et al. 1999). After oral ingestion of 250 ml of tea in volunteers, the level of L-TH reached a peak plasma concentration of 26.5 µmol/L

at 0.8 h (Scheid et al. 2012). Part of L-TH absorbed by the intestine is retained in red blood cells, and most of the rest is hydrolyzed into glutamate and ethylamine, and a small amount is discharged in the original form. The retention time of L-TH was 10 mins, and the subjects reached the maximum plasma concentration (1.0–4.4 mg/L) after 50 mins (van der Pijl, Chen, and Mulder 2010).

The intestinal absorption of L-TH was mediated by sodium-coupled cotransporters in the brush boundary membrane (Kitaoka et al. 1996). Therefore, oral L-TH is efficiently absorbed from the gut and delivered to the brain across BBB (Kakuda 2011). In addition, L-TH was also reported to be carried through the intestine through the methionine carrier transport system. The absorbed L-TH is transported through the blood to the main organs, mainly the brain. It can then be excreted directly through urine or hydrolyzed and catabolized into glutamate and ethylamine in the kidney, and then it can also be excreted from the body with urine (Vuong, Bowyer, and Roach 2011).

Effects of L-theanine on AD

Kakuda (2011) reported that the cognitive impairment of elderly volunteers was improved after eating powdered green tea containing high theanine concentration. On the other hand, theanine fed rats showed better recognition ability to affect learning and memory (Yamada et al. 2008). The positive effect of L-TH on cognitive ability is one of its most important functions. The chemical structure of L-TH is similar to glutamate, and therefore it can act as a neurotransmitter related to memory (Türközü and Şanlier 2017). Firstly, it is pointed out that L-TH penetrates the BBB and shows brain protection, preventing neuronal cell death after transient cerebral ischemia. This neuroprotective effect is partly caused by the antagonistic effect of glutamate receptor on its subtype AMPA and hole receptor. In addition, L-TH inhibits the combination of extracellular glutamine and neurons as it is a glutamine carrier (Kakuda 2011). It was reported that L-TH promoted neurogenesis and enhanced the proliferation of precursor cells of the nervous system, suggesting that L-TH can be used as part of neuronal regeneration therapy for AD (Abe et al. 2007).

The potential regulatory mechanism of L-TH on AD is attributed to its antioxidant ability and its unique effect of antagonizing glutamate. Ben et al. (2016) found that L-TH inhibited Cd-induced tau protein hyperphosphorylation on Ser199, Ser202 and Ser396, and that L-TH inhibited GSK-3β activation, which leads to tau hyperphosphorylation and Cd-induced cytotoxicity. In addition, L-TH may protect neurology by interfering with the protein kinase B/mammalian target of rapamycin (Akt/Mtor) signaling pathway. L-TH may modulate hippocampal synaptic efficacy and improve AD symptoms through the dopamine D1/5-PKA pathway (Zhu et al. 2018). L-TH can alleviate Aβ-induced oxidative stress and activate ERK1/p38MAPK and NF-κB pathways to inhibit neuronal cell death (Kim et al. 2009). Furthermore, L-TH showed anti-neurotoxicity induced by L-glutamate on APPsw-overexpressing SH-SY5Y cells by overactivating the NMDA receptor and its associated pathways (Di et al. 2010). As a natural antagonist of glutamate, L-TH can prevent the increase of Aβ secretion caused by excessive activation of NMDA receptors, regulate Ca^{2+}- and NO-related cell signaling pathways, and protect nerve cells from apoptosis (Di et al. 2010). L-TH also shows anti-inflammatory effects by reducing the expression of the inflammation-related factors TNF-α and IL-1β (Park et al. 2018). Generally, similar to EGCG and caffeine, L-TH can reduce Aβ expression, aggregation and tau phosphorylation, eliminate AB plaque, clear ROS and regulate inflammatory factors. The difference is that L-TH has a prominent effect on cholinergic, and its natural antagonism against glutamate highlights the neuroprotective effect of L-TH.

The safety of L-TH

The safety of L-TH has been confirmed by Liu et al. (2021). The NOAEL for L-TH was 4000 mg/kg/day in rats (Borzelleca, Peters, and Hall 2006). L-TH is also certified as generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (FDA). Meanwhile, the FDA pointed out that the maximum daily consumption of L-TH is 1200 mg (Vuong 2014).

Other active compounds

As the second non-protein amino acid that contributes to the function of tea (Yu and Yang 2020), GABA is one of the two major inhibitory neurotransmitters in the CNS (Bowery and Smart 2006). GABA may be the key to a complex system of factors that leads to the main clinical feature of AD: episodic memory loss (Jiménez-Balado and Eich 2021). Excessive GABA play an important role in a variety of neurological diseases such as anxiety, depression, and insomnia. The dysfunction of GABAergic receptor can lead to mood and depressive disorders. The GABA content in the brains of AD patients tends to decrease (Fuhrer et al. 2017; Gueli and Taibi 2013), and GABA in tea can fix this insufficiency. Nevertheless, there have also been reports of increased GABA levels in the hippocampus and cerebrospinal fluid of AD patients (Jo et al. 2014). Therefore, before exploring drugs targeting GABAergic neurotransmission as a potential therapy for AD, a common consensus on GABA changes during AD progression remains to be determined (Roy et al. 2018).

PQQ has a strong antioxidant capacity to scavenge free radicals, which is 50–100 times higher than that of ascorbic acid. Derivatives of PQQ can protect neurons by scavenging free radicals and inhibiting peroxidation through the BBB (Murray 2020; Akagawa, Nakano, and Ikemoto 2016). A novel multifunctional compound named Camellikaempferoside B (YCF-2) was isolated from Fuzhuan tea. YCF-2 is composed of a new structure of kaempferol backbone, p-coumaric acid (p-CA) group and a rhamnopyranoyl group at the C-4′ position with the properties of kaempferol and p-βCA. YCF-2 could inhibit $Aβ_{42}$ fibrillation and promoted the formation of nontoxic oligomers by binding to $Aβ_{42}$ oligomers and by blocking the conformational transition to β-sheets. Furthermore, YCF-2 ameliorated Aβ-induced neuronal cell

death by blocking the NF-κB signaling pathway in microglia, and inhibited ROS production, inflammatory factor release, and microglial activation (Yang, Jin, et al. 2016).

Potential mechanism of tea active ingredients in AD improvement

The occurrence of AD is influenced by a variety of interactive factors. Specifically, the generation and aggregation of Aβ and the hyperphosphorylation and aggregation of tau promote each other, which in turn leads to neuroinflammation and oxidative stress. The phenomenon further aggravates the symptoms of AD and the aggregation and neural tangles of Aβ. Therefore, tea active ingredients can mainly regulate AD through the following potential mechanisms (Figure 4).

Inhibit the expression and aggregation of Aβ

EGCG can elevate α-secretase activity and reduce β- and γ-secretase activity by inhibiting the ERK/NF-κB pathway to reduce APP levels and Aβ production (Lee et al. 2009). Caffeine stimulates PKA activity and reduces the overactive form of c-Raf-1, thereby inhibiting NF-κB pathway and β-secretase expression to reduce Aβ production (Zhou and Zhang 2021). Similar to EGCG and caffeine, L-TH reduces Aβ plaques in the hippocampus and cortex as well as down-regulating BACE1 activity (Zhu et al. 2018; Kim et al. 2009). Unlike EGCG, which activates autophagy to reduce Aβ deposition (Rezai-Zadeh et al. 2008), ECG and EGC can alleviate Aβ aggregation mainly by chelating metal ions (T. Chen et al. 2020). Caffeine also reduces ApoE polymorphism levels (Zhou and Zhang 2021), and EGCG promotes NEP secretion through ERK and phosphatidylinositol 3-kinase (PI3k)/PKB (PKB = AKt) pathways to reduce the level of Aβ aggregation (Chang et al. 2015). In general, the active components of tea seal the source of Aβ by reducing the activity of β- and γ-secretase through ERK/NF-κB signal pathway. Thereafter, tea active ingredients can reduce the existing Aβ by increasing the activity of α-secretase, activating autophagy and reducing the level of ApoE polymorphism to prevent and treat AD.

Inhibit the hyperphosphorylation and aggregation of tau

Hyperphosphorylation of tau protein leads to NFTs intracellular aggregation. Aβ-mediated Tau phosphorylation has also been reported (Edwards 2019). The p-Tau protein is deeply related with neurological dysfunction, such as disrupting microtubule networks and axonal transport or cell signaling (Guo, Noble, et al. 2017). Thus, decreasing the levels of hyperphosphorylation of tau can be used as one of the therapeutic targets for AD. GSK-3α and GSK-3β are closely related to reducing tau hyperphosphorylation. EGCG, caffeine and L-TH all inhibit tau hyperphosphorylation, while EGCG inhibits GSK-3β by attenuating TNF-α/c-Jun signaling, thereby reducing phosphorylation levels (Jia et al. 2013). Caffeine inhibits phosphorylation by reducing the dysregulation of GSK-3α expression (Zhou and Zhang 2021). In addition, caffeine can reduce phosphorylation by antagonizing the coupling of $A_{2A}R$ to G proteins (Dias et al. 2013), and L-TH reduces tau phosphorylation by inhibiting GSK-3β and Akt/mTOR (Ben et al. 2016).

Inhibition of neuronal apoptosis

Apoptosis plays a key role in the progression of AD (Radi et al. 2014), which is associated with DNA fragmentation, chromatin condensation, TNF-α, ROS, Aβ, perturbation of enzymes factors, activation of cysteine-proteases and caspases(Radi et al. 2014; Yang, Ren, et al. 2021). Inhibiting
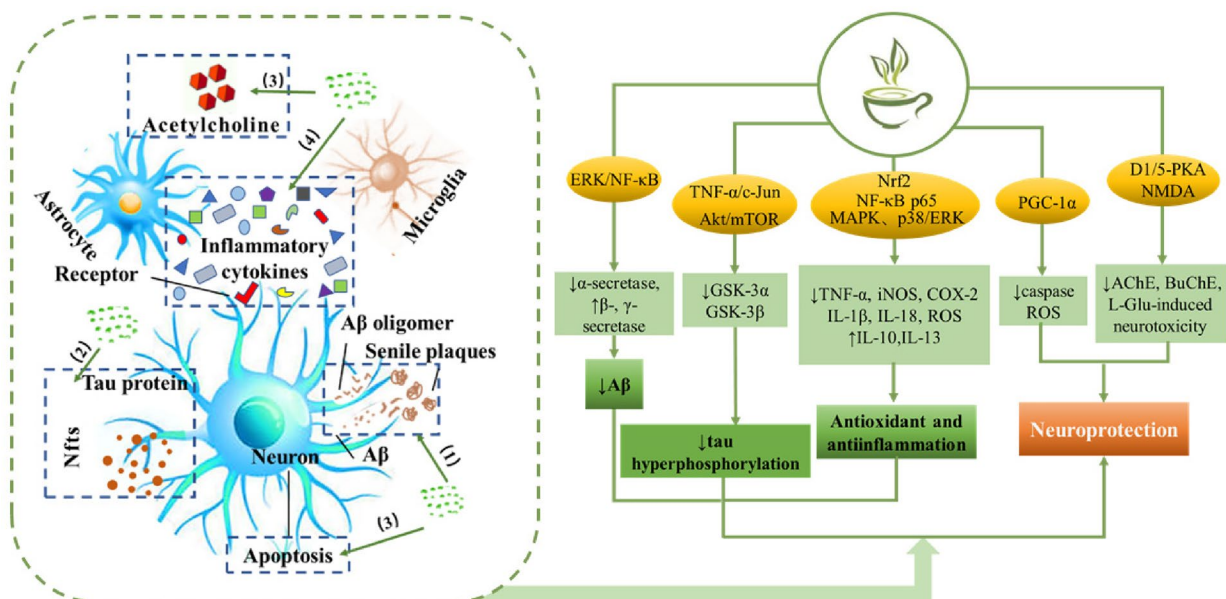

Figure 4. Mechanism of active components in tea to modulate AD.

apoptosis could be considered as the preventive and therapeutic strategy for AD. EGCG, caffeine and L-TH can prevent or inhibit caspase activation, calcium homeostasis disorder and excitatory toxicity caused by neurotransmitter imbalance, synaptic plasticity disorder and neuronal dysfunction, and play a role in protecting the nervous system. EGCG can inhibit the activation of caspase-3 by increasing the expression level of PGC-1α (Zhang et al. 2017). EGCG, ECG and EGC can chelate metal ions to prevent neurotoxicity caused by deposited metal ions (Chen, Shi, et al. 2020). EGCG can also suppress endoplasmic reticulum stress-related neuronal apoptosis (Du, Liu, et al. 2018). Caffeine reduces the damage to mitochondrial electron transport by reducing the formation of ROS to prevent the activation of caspase-3 (Dragicevic et al. 2012). L-TH can inhibit caspase activation induced by L-glutamate (Di et al. 2010). PQQ derivatives can improve metabolic circulation through BBB to effectively protect neurons (Murray 2020).

Regulation of neurotransmitters

Acetylcholine (ACh) is an important neurotransmitter used by cholinergic neurons, participating in several crucial physiological processes, such as attention, learning, memory, stress response, arousal and sleep, and sensory information. Cholinergic neuron injury is considered to be a key pathological change associated with cognitive impairment in AD (Du, Wang, et al. 2018; Haam and Yakel 2017). In terms of neurotransmitters, EGCG, caffeine and L-TH can reduce the activity of acetylcholinesterase and increase the level of acetylcholine. EGCG and caffeine competitively inhibited acetylcholinesterase AChE and BuChE (Biasibetti et al. 2013; Pohanka and Dobes 2013). In addition to inhibiting AChE, L-TH can also activate NMDA receptor, antagonize the neurotoxicity caused by L-glutamate (Kim et al. 2008), and regulate the synaptic efficiency of hippocampus through dopamine D1/5-PKA pathway to play a neuroprotective role (Zhu et al. 2018; Di et al. 2010).

Antioxidant and anti-inflammatory capacity

EGCG, caffeine and L-TH can inhibit activation of neuroinflammation through microglia and astrocyte and elevation of pro-inflammatory factors and inflammatory proteins such as TNF-α, iNOS and COX-2. EGCG reduces pro-inflammatory factors by inhibiting NF-κB p65 transport and Iα degradation (Zhang et al. 2017). Meanwhile, EGCG can upregulate the levels of anti-inflammatory factors (IL-10 and IL-13) and reduce the expression of pro-inflammatory factors (IL-1β and IL-18) (Bao et al. 2020; Zhong et al. 2019). In addition, EGCG can activate Nrf2, which acts as an antioxidant and reduces the production of ROS (Scapagnini et al. 2011). Caffeine can suppress the formation of ROS to reduce the damage to mitochondrial electron transport (Dragicevic et al. 2012). L-TH can activate MAPK, p38/ERK and NF-κB pathways to reduce protein and lipid oxidative damage and ROS production (Kim et al. 2009). In terms of anti-inflammation, L-TH reduces the expression of TNF-α

and IL-1β (Park et al. 2018). Moreover, PQQ shows a powerful antioxidant capacity to clear ROS and inhibit peroxidation (Murray 2020; Akagawa, Nakano, and Ikemoto 2016). Similarly, YCF-2 can inhibit ROS production, inflammatory factor release and microglia activation by blocking the NF-κB signaling pathway in microglia (Yang, Jin, et al. 2016).

Gut microbiota

Gut microbiota is closely related to diet. As shown in Figure 5, previous studies have shown a tight and varied association between gut microbiota and AD (Haran et al. 2022; La Rosa et al. 2018; Jeon et al. 2019; Kim et al. 2020; Hang et al. 2022). Gut (La Rosa et al. 2018; Jeon et al. 2019), gut microbiota (Kim et al. 2020), and metabolites of gut microbiota (Hang et al. 2022) have different effects on AD by affecting gut permeability, gut hormones, immunity, genetic material, inflammation, oxidative stress, neuroprotection and metabolism (Hang et al. 2022). For instance, the reduced abundance of gut microflora is strongly associated with neurodegeneration, thereby inducing inflammation to aggravate AD (Fung, Olson, and Hsiao 2017; Qian et al. 2021). Zhang et al. (2013) pointed that EGCG, GCG and EGCG3"Me promoted the growth of Bifidobacterium spp. and Lactobacillus/Enterococcus groups and exhibited inhibitory effects on the growth of Bacteroides–Prevotella, Clostridium histolyticum and Eubacterium–Clostridium groups. Zhang et al. (2021) found that Pu-erh tea extract could alleviate intestinal inflammation through promoting the growth of intestinal probiotics and inhibiting pathogenic bacteria. Tea extracts changed the overall composition of gut microbiota and decreased the relative abundance of Rikenellaceae and Desulfovibrionaceae (Liu et al. 2019). In addition, Fuzhuan brick tea polysaccharide was reported to alleviate inflammation and disruption of the intestinal microbiota, promote the proliferation of beneficial microbiota such
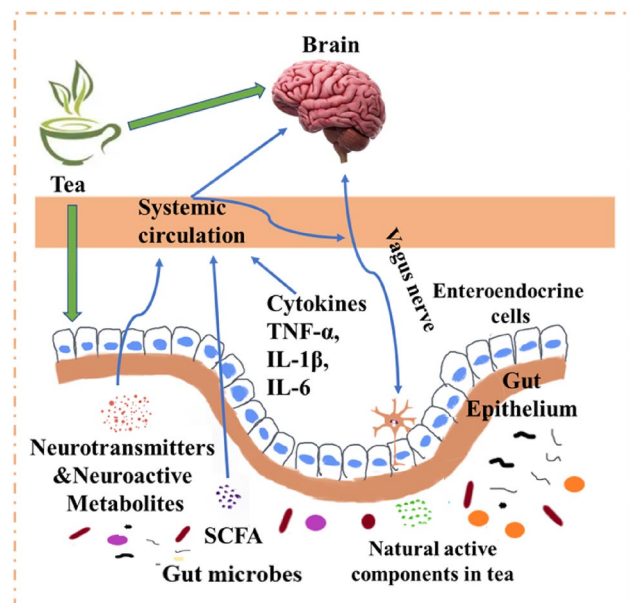

Figure 5. Mechanism of tea active components on affecting AD through gut microbiota.

as *Lactobacillus* and *Ackermannia*, and significantly increase the levels of short-chain fatty acids (Yang, Ren, et al. 2021). The metabolites of gut microbiota also contribute to the removal of misfolded proteins (Bonfili et al. 2017). The fluctuations in the bacterial profile affect the afferents of vagal nerve fibers and alter neurotransmitter levels in the brain (Bostanciklioğlu 2019; Goehler et al. 2005). Tea active ingredients can directly modulate microbial composition, microbial community function, and their metabolites. Due to the existence of BBB, most tea active ingredients can only indirectly affect brain function through the enteric nervous system due to the bidirectional action of the gut-brain axis except caffeine and L-TH. A small amount of tea active ingredients that are catabolized in the gut will release small molecular compounds, which can exert a preventive role by inhibiting the aggregation of Aβ, regulating and improving oxidative stress and neuroinflammation to alleviate neurotoxicity.

Conclusions and perspectives

The health benefits of drinking tea have been recognized around the world. Most epidemiological surveys show that drinking two or three cups of tea a day, especially green and black tea, can reduce the risk of cognitive impairment. The neuroprotection of tea is a research hotspot in the field of tea and health in recent years. The neuroprotective effect of tea exhibits the advantages of multiple targets, nontoxicity and good synergy. Due to the complex pathological mechanisms of neurodegenerative diseases, multi-target therapeutic strategies have gradually become a trend, and tea can exert neuroprotective effects through multi-component interactions. In vivo and in vitro studies have shown that TPP, L-TH, caffeine, and other tea active substances have shown neuroprotective effects on AD.

The regulation of AD by active ingredients in tea can be divided into direct effect and indirect effect. In terms of direct effect, the tea active ingredients absorbed by the intestine can act on the nervous system and immune system, including the following aspects: (1) By regulating signaling pathways or abnormal kinases, increasing the activity of α-secretase and reducing β-, γ-secretase makes APP produce less Aβ. Meanwhile, the tea active ingredients promote the degradation of Aβ and reduce plaques in the brain. (2) The tea active ingredients can reduce GSK-3α and GSK-3β to inhibit tau aggregation and hyperphosphorylation, which reduces NFTs in the brain. (3) The active ingredients of tea can prevent or inhibit the activation of caspase, calcium homeostasis disorders and excitotoxicity caused by neurotransmitter disorders, synaptic plasticity disorders and neuronal dysfunction, which can inhibit neuronal apoptosis and protect the nervous system. (4) The active ingredients of tea can inhibit acetylcholinesterase AChE and BuChE, regulate hippocampal synaptic efficacy through dopamine D1/5-PKA pathway, and activate NMDA receptors to antagonize the neurotoxicity of L-glutamate. (5) The active ingredients of tea inhibit the neuroinflammation activated by microglia and astrocytes and the increase of pro-inflammatory factors and inflammatory proteins, thereby alleviating the aggregation of Aβ and the phosphorylation of tau, and protecting the brain nerves. Indirect effects represent that some active ingredients of tea are not effectively absorbed by small intestine, but can be adequately utilized by gut microbes after entering the colon to potentially affect AD in several ways such as gut permeability, gut hormones, immunity, genetic material, inflammation, oxidative stress, neuroprotection and metabolism through the gut-brain axis.

There are still some limitations in the research on the regulation of AD by tea and its active ingredients. First, the current research mainly focuses on EGCG in TPP, and the research on other tea active ingredients is insufficient. Taking L-TH as an example, although there exists evidence that L-TH can inhibit the formation and aggregation of Aβ and the phosphorylation of tau, its specific molecular mechanism remains unclear. Similarly, other tea active ingredients are in the same predicament. Second, the low bioavailability of TPP hinders exerting their biological activity (Rashidinejad et al. 2021), which are attributed to poor stability, passive diffusion, and active efflux in the gastrointestinal tract (Liang et al. 2017). Presently, some strategies have been proposed to improve the bioavailability of TPP through nano-delivery technology (Rashidinejad et al. 2021). Smith et al. (2010) enhanced the oral bioavailability of EGCG through lipid nanoparticles, which could elevate neuronal α-secretase by up to 91%. Therefore, the use of nanotechnology to modify TPP or other active ingredients to improve bioavailability can be an alternative. Finally, there are some problems to be explored on the indirect regulation of AD by tea active ingredients through gut microbiota. For instance, what is the specific mechanism of the interaction between microbial neurotransmitters and the nervous system? There is still no report on the influence of tea polysaccharides on AD. It is noteworthy that previous studies have proposed a mechanism to modulate AD through intestinal flora (Cattaneo et al. 2017; Marizzoni et al. 2017; Bostanciklioğlu 2019), and tea polysaccharides have shown the ability to regulate intestinal flora. Therefore, the effects of tea polysaccharides on AD via intestinal flora should be confirmed. TPP, L-TH and caffeine, which have shown direct effects on AD, can also be further investigated through the intestinal flora.

In general, the signaling pathways that regulate AD are not limited to a single disease. EGCG, caffeine, L-TH and YCF-2 can regulate AD through the NF-κB pathway, which has been reported to be an inflammation-related pathway that regulates inflammatory diseases such as pulmonary fibrosis, asthma and pneumonia (Alharbi et al. 2022). The PKA pathway, which enables caffeine and L-TH to regulate AD, also plays a role in maintaining metabolic health (London and Stratakis 2022). The NRF-2 pathway is closely associated with oxidative stress-related diseases (Cen et al. 2022). The activation of mitogen-activated protein kinases (MAPKs) (ERK1/2 and p38 MAPKs), is linked to cell proliferation, differentiation, motility and survival (Roux and Blenis 2004). Different diseases can be regulated by the same pathway, which suggest new targets for the prevention and treatment of AD or similar diseases.

Considering that the majority of antineoplastic drugs produced are derived from natural products or their semi-synthetic or synthetic derivatives, accounting for approximately 80% in the last three decades, the potential of plant metabolites in the development of new therapeutics is clear (Newman and Cragg 2016). Metabolites of natural products have low toxicity and high bioactivity potential. Of the 250,000 known plant species, only 5–15% have been developed for their biological activity (Majolo et al. 2021). Bioactive compounds have been used for centuries but have not been fully elucidated (Majolo et al. 2021). In addition to their individual effects, the synergistic effects of several natural active ingredients remain to be systematically explored. The effect of single active component of tea on AD is the basis of the physiological activity of tea drinking to prevent and regulate AD. Difference teas contains active ingredients of varied chemical compositions and contents. Therefore, future research must clarify the effects of different combinations of tea active ingredients on AD and their associated health benefits and potential risks. Based on the dose-response relationship, further research can provide scientific guidance for the development of different tea active ingredients and tea drinking to ameliorate AD. For instance, the combination of L-TH and caffeine can improve attention (Einöther et al. 2010), and L-TH may also improve some of the side effects of caffeine intake, such as reversing caffeine-induced slow-wave sleep reduction (Jang et al. 2012). EGCG could reverse the anxiolytic effects induced by caffeine (Park et al. 2010). In addition to this, the combined use of EGCG and L-TH with other bioactive ingredients outside of tea such as ginkgo biloba, resveratrol, cocoa, tobacco, saffron, and curcumin also exhibit positive effects on cognitive impairment (Cicero, Fogacci, and Banach 2018). In the future, the effects of the combination of natural active ingredients on AD remains to be further explored.

Acknowledgements

Authors' contributions statement

Yi Huang and Yang Wei: Conceptualization, Writing-Original draft preparation and Revision (contributed equally to this work). **Jia Xu:** Investigation and Methodology. **Xinlin Wei:** Supervision, Reviewing and Editing.

Disclosure statement

Funding

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