Several Key Health Benefits of Tea Polyphenols

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Abstract: Tea polyphenols are believed to have multiple health benefits to humans. Tea polyphenols have the function to inhibit cancer, which mainly depends on three different pathways. Cancer can be inhibited by tea polyphenols through inhibiting the formation of cancer cells, blocking the spreading of cancer, and inducing the cancer cells to destroy themselves. Tea also has beneficial effects on inhibiting Alzheimer's disease through the anti-beta-amyloid effect and other mechanisms like preventing tau phosphorylation and aggregation. The last two parts discussed tea polyphenols play a role in antibiosis and anti-inflammatory by some detailed mechanisms. Though tea polyphenols have many beneficial effects, some of the mechanisms of these effects have remained unclear. Further studies need to be carried out to figure them out.

1. Introduction

Tea is one of the most famous beverages throughout the world. Tea contains many bioactive compounds that are beneficial for health, and tea polyphenol is one category. In terms of green tea, what take up the majority of tea polyphenols are called catechins, such as (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epicatechin (EC), as shown in Figure 1. These compounds are reported with various health benefits which mainly because of their antioxidant and anti-inflammation ability. TF possesses the antioxidant effects is mainly because of its ability to scavenge free radicals. The radical-scavenging ability has been mainly attributed to phenolic groups and the antioxidant ability is enhanced accompanied with the increase of the numbers of phenolic groups. TP's main health benefits include anti-cancer property, immune system enhancement and prevention of Alzheimer's disease.
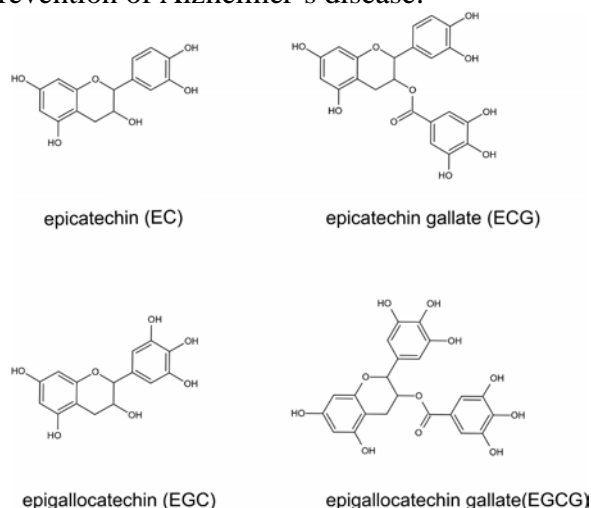

Figure 1. The chemical structures of main catechins in tea.

2. Inhibition of cancer

In China, traditional Chinese medical believes that tea has the function of anti-aging, anti-cancer and hence is good for health. As the study on the functions of tea goes further, the main beneficial compounds that can inhibit cancer are gradually revealed.

Research show that tea polyphenols can inhibit carcinogenesis, such as cancers of the skin, lung, esophagus, stomach, liver, duodenum, small intestine, pancreas, colon, bladder, prostate and mammary gland [1]. Tea polyphenols function their anti-cancer properties in different ways, like inhibiting carcinogenesis, which stops the formation of cancer (Figure 2); block the proliferation, which prevents the spread of cancer (Figure 3); inducing apoptosis of cancer cell lines, which directly eliminates cancer cells (Figure 4).
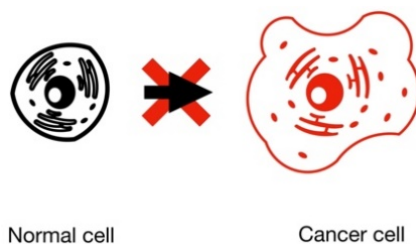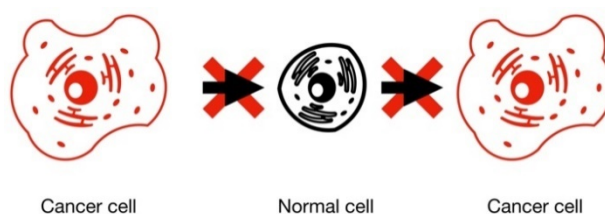
Figure 2. Inhibition of carcinogenesis.

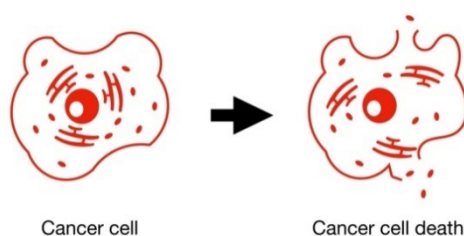Figure 3. Inhibition of proliferation.

Figure 4. Induction of apoptosis.

2.1 Inhibition of carcinogenesis

There are various ways for substances to function anti-cancer properties, and what strikes first is to solve the problem from the very beginning. Carcinogenesis is the process that cancer cell starts to form, as a result of intrinsic factors such as immune diseases, endocrine abnormal and hereditary factor, or extrinsic factors like smoking, biological infection and intoxication, as well as radiation. Research points out that, tea polyphenols are able to prevent carcinogenesis. In one study, it is said that if tea is consumed continuously for a period, tumor-initiating clone may be inhibited, leading to the prevention of carcinogenesis progression [2]. Research points out that, after 16 weeks of the injection of NNK (4-(methylnitrosamino)-1-(3-pyridyl-1-butanone), almost all the mice developed adenomas. When these mice were given black tea that contains theaflavins, the development of tumors into adenocarcinomas were inhibited [3]. Hence, it is obvious that tea polyphenols are able to prevent the formation of cancer cells and are good source in terms of cancer precaution. However, the specific mechanism of how tea polyphenols inhibit carcinogenesis still require further study.

2.2 Inhibition of proliferation

As cancer cells are generated, the adhesion among these cells is lowered. Cancer cells then separate themselves from other cells, and transfer into circulation system such as blood vessels or lymph

vessels. Then cancer cells can be transferred into other organs of the body, producing more cancer cells, spreading the cancer to other parts of the body. This spreading of cancer cells is called proliferation. Therefore, besides preventing cancer by inhibiting it arise, it is also a good method to block the proliferation of cancer cells. As cancer cells spread in a much slower rate, it will be easier to target and cure the cancer.

For instance, lung cancer takes up the most portion of cancer-related deaths throughout the world [4]. One of the reasons is that there is an increasing number of people who smoke. Many compounds in cigarettes such as nicotine and nitrosamines, are considered as carcinogens. These carcinogens may lead to lung cancer. Besides smoking, air pollution, lung diseases may also contribute to lung cancer.

It is good news that tea polyphenols such as theaflavin (TF) and EGCG are able to inhibit proliferation of lung cancer. Compared to bulk polyphenols, TF/EGCG -loaded PLGA-NPs (theaflavin and EGCG -loaded lactide-co-glycolide nanoparticles) can lower IC50 (half-maximal inhibitory concentration, used to measure a drug's efficiency) doses greater, indicating the key functioning compounds in proliferation of lung cancer cells [5].

Another cancer, called colorectal cancer (CRC), is notorious as it is a prevalent cancer. EGCG, combined with radiation treatment, is said having the ability to inhibit the proliferation of CRC according to one study [6]. EGCG can inhibit proliferation as well as suppression the expression of H3K27me (methylation of lysine 27 on histone H3) in RKO (poorly differentiated colon carcinoma cell line) CRC cells together with GSK343 (a potent and selective EZH2 inhibitor).

2.3 Induction of apoptosis

Apoptosis is a kind of programmed cell death. This is cell death is a controlled and beneficial process which is good for the organism, which helps to clean up damaged cells. As cancer cells are cells that we want them to be removed, it is a good idea to lead to apoptosis of these cancer cells. Unlike other regular cancer treatment which kills both healthy cells and cancer cells, apoptosis will only result in the death of cancer cells, not harming the good cells.

Tea polyphenols are able to induce the apoptosis of cancer cells. In other words, cancer cells can be removed through treatment with tea polyphenols, as cancer cells destruct themselves.

An in-vitro study suggests that EGCG and EGC are able to induce the apoptosis of lung tumor cell, though EGC is less effective than EGCG [7]. A cytotoxic effect is found in the tests, and this apoptosis effect is believed to be the major mechanism for cell killing in a certain concentration of tea polyphenols.

Prostate cancer (PCa) is a common cancer in males. Green tea polyphenol EGCG can sensitize LNCaP cells to TRAIL-mediated apoptosis in prostate cancer [8]. The most important factor in this apoptosis process is that the recruitment of FADD (Fas Associated Via Death Domain) downstream, which follows the activation of death receptor by TRAIL (a cytokine that produced by most tissue cells), resulting in the final cell death.

3. Tea And AD

As the population ages, Alzheimer's disease (AD) has becoming more and more ubiquitous. In terms of the symptoms, AD causes severe suffering for patients, including progressive memory loss with difficulty in performing daily activities, lack of coordination, social withdrawal, vision problems, and poor judgment [9]

However, AD's pathogenetic mechanisms are complex and there is no solution to cure it thoroughly. Although molecular mechanisms have not been fully understood, a growing corpus of researches show that AD pathophysiology is mainly associated with the hyper phosphorylated protein tau neurofibrillary tangles (NFT) and extracellular amyloidal beta (Aβ) protein deposits, which further affected specific areas of the brain that control memory and cognitive function through oxidative stress or inflammation [10].

At the same time, tea gain much attention as adjuvant therapy for various neurodegenerative diseases including AD because of its structure characteristics, which has been confirmed by numerous

evidence both in the vitro and vivo levels. However, tea effects on anti-inflammation and anti-oxidative stress are highly dependent on the contents while the epidemiological evidence between tea consumption dose and AD are insufficient. Thus, more studies are needed to find the relationship between doses and AD prevention.

3.1 In molecular levels

Many studies have showed that TP prevent AD by way of antioxidant, anti-inflammation, prohibition of tau phosphorylation and aggregation, inhibition of Aβ aggregation etc. [11].

3.1.1 Anti-beta-amyloid effect

Beta-amyloid peptides were generated from amyloid precursor proteins after cleaved by alpha-, beta- and gamma- secretase [9].

The processing of amyloid precursor proteins produced beta-amyloid peptide 1–42, which is neurotoxic and is the characteristic of Alzheimer's disease. Beta-amyloid peptide 1–42 further contributes towards inflammation, elevate expression levels of pro-apoptotic proteins, iron accumulation and oxidative stress, which further harms the neuro cells [12]. Therefore, it is a way to prevent AD through inactive the enzymes related to Aβ42 formation. A study validated that the application of EGCG can act as inhibitors of β-secretase and γ-secretase to reduce the production of Aβ42 through regulation of Ach level [13].

What's more, more and more researches also showed that TF can play an effective role in alleviating the neurotoxicity of Aβ42 to prevent AD. On the one hand, a study demonstrated that EGCG protects neuronal cells against fibrillar Aβ-evoked neurotoxicity by rendering preformed fibrils into an inactive, non-toxic form. And EGCG achieved that through the stabilization and modification of amyloidogenic proteins coupled with the interaction with Aβ hydrogen. On the other hand, it is also documented that EGCG induced dissociation of fibrils to protect neuronal cells [12].

Furthermore, TP exerts a neuroprotective role in AD through regulation of cell signaling pathways induced by Aβ42. Results shows that TPs can protect neurons against Aβ-induced neurotoxicity and normalize the dysfunction of neuroprotective Akt signaling pathway caused by Aβ42, indicating that TP show potentials in the treatment for Alzheimer's disease [12]. Another study also showed that EGCG mitigated oxidative stress in SH-SY5Y cells induced by Aβ42 through regulating the levels of Bax, bcl2 and caspase-3 [14].

In Alzheimer's disease mouse models, EGCG could alleviate learning and memory deficits and reduced the over-expressions of Aβ (1–40) and amyloid precursor protein (APP) [9]. What's more, application of Epicatechin (50 mg/kg daily for 4 months) combined with treadmill exercise could protect cognition-impaired mice against cognitive deficits through lowering soluble Aβ42 levels [11]. Study also demonstrates that intraperitoneally administration of EGCG in 12-month-old AD model mice reduced insoluble Aβ1– 40, 42 level by 47% inversely associated with an about 40% increase in A-secretase cleavage activity [10].

3.1.2 Other mechanisms

It is indicated that the enhancement of antioxidant ability in body is associated with a lower possibility of Alzheimer's disease.

Study shown that green tea polyphenols protected against glutamate induced neurotoxicity in the cortical neurons by attenuation of oxidative stress and antimitochondrial apoptotic pathway [15].

What's more, EGCG plays a crucial role in preventing tau phosphorylation and aggregation, which further inhibits neuronal cell death [11]. On the one hand, TPs inhibit tau beta-sheet formation and bind to phosphorylation sites such that access by kinases is diminished thus can prevent the aggregation of tau [16]. On the other hand, EGCG enhances the clearance of AD-relevant phosphorylated tau species by enhancing expressions of two autophagy receptor proteins [12]. At the same time, EGCG could transiently bind rare oligomers and catalytically return tau to its unfolded monomeric state [16].

In terms of AD's animal models, Guo et al. reported that long-term oral consumption of EGCG at a relatively high dose (15 mg/kg) ameliorated the impaired working memory and spatial learning memory in AD model mice [17].

3.2 Epidemiological Evidence

Many studies showed that drinking tea is related to a lower risk of cognitive impairment. For example, a cross sectional study based on the adults age$\geqq$55 in a Singapore community showed that tea consumption was associated with a better physical and functional performance.[18] What's more, another cross-sectional study among 1003 Japanese people aged>70 y has revealed that higher consumption of green tea is related to a lower prevalence of cognitive impairment [19]. Additionally, a meta-analysis of 26 observational studies has shown that tea drinking is associated with decreased risk of cognitive decline in the elderly [20].

Furthermore, the result of cohort study including 13, 5645 participants showed that green tea consumption is significantly associated with a lower rate of incident dementia [21]. However, there are some studies showed no relation between tea consumption and the prevention of Alzheimer's disease. A meta-analysis study showed that it is no evidence for drinking green to be protective against AD [22]. A cross-sectional study also showed that to reach the ideal anti-neurodegeneration effects of green tea, higher amounts is needed compared with the previous studies [23].

In conclusion, tea consumption might have the beneficial effects against the Alzheimer's disease.

4. Antibiosis

4.1 Mechanism for antibiosis of tea polyphenols

In the present studies, there have been some researches talking about the mechanisms of antibacterial action of polyphenols. Some investigations have indicated that catechins adhere to the cell envelope of Gram-positive and Gram-negative aerobic bacteria. Another study indicated that catechins respond to dissolved oxygen and generate hydrogen peroxide, having bactericidal action on bacteria. Totally, tea polyphenols have the following antibacterial mechanism: Changing the normal physiological morphology of thallus; destroying the activity and permeability of enzyme system on cell wall membrane; inhibiting thallus protein built and expressed and affecting the genetic characteristics of bacterial DNA [24].

As table 1 shown the application points about antibacterial, there are some relevant studies can declare these.

A study showed that EGCG made some cells elongated or ruptured rather than those without EGCG, having intact and smooth surface. And these elongated cells only survival serve hours and eventually dies [25]. Other study showed that tea polyphenols can cause corruption shewanella spp cell wall and cell membrane damage, increase the cell membrane permeability, and change the cell morphology, make the intracellular enzyme leakage, the bacteria in the body material transport, energy conversion, information transmission and other normal physiological and metabolic disorders, from which can cause bacteria to become less active and even die. Through TEM, SEM observation, with tea polyphenols, the number of bacteria gradually decreased, while Extracellular supernatant of Na + / K + ATPase and AKP activity increased significantly.

Catechins alter the permeability of bacterial cell membranes, causing proteins inside the cells to leak into the culture fluid outside the body.

The effect of tea polyphenols on staphylococcus aureus for 1~3 h severely blocked the expression of thallus protein, and then destroyed the enzyme activity and thallus structure, resulting in the loss of normal physiological activity of thallus. But there have been few studies on how tea polyphenols inhibit bacterial protein expression.

When tea polyphenols mixed with DNA, it gave an exothermic signal, which indicates that tea polyphenols can interfere with bacterial genetic characteristics through its interaction with DNA to achieve its effect.

Table 1. Mechanism for antibiosis.

Application point	Effect
Normal physiological morphology	cell wall and cell membrane damaged
Enzyme system	the permeability of bacterial cell membranes altered
Thallus protein	the expression of thallus protein blocked
Bacterial DNA	interfering with genetic characteristics

4.2 Antibacterial action

So far, there are several researches reported that tea polyphenols, from some different kinds of tea, all can inhibit E. coli, staphylococcus aureus and Bacillus subtilis. With the same kind of tea, but in different concentration of tea polyphenol, the dose of tea polyphenol is correlated with inhibition of the same culture, and staphylococcus aureus are most obviously.

Tea polyphenols can act on E. coli cell membrane and DNA, changing the permeability of cell membrane and affecting the genetic function, to exert antibacterial effect.

Tea polyphenols can reduce the activities of alkaline phosphatase and adenosine triphosphate enzyme in bacteria, and has no obvious effect on total protein of bacteria, but has a significant effect on membrane protein of bacteria, suggesting that tea polyphenols can disrupt bacterial metabolism, destroy cell structure, and thus play an antibacterial role.

4.3 Application

4.3.1 Regulation on intestinal flora

There is a very complex microbiome in the gastrointestinal tract of humans and animals. The number of bacteria in a normal adult's gut is 1014, about 10 time's number of somatic cells totally. The number of genes in the gut microbe genome is 100 to 150 times that of the human genome [26, 27]. Henning et al. reported that decaffeinated green tea and black tea polyphenols can regulate intestinal flora and reduce weight in diet-induced obese mice [28]. Some studies have shown that tea polyphenols have a good regulation effect on the dysregulation of bacterial community. Studies on the effects of catechin on the growth of intestinal microflora showed that methylated catechin could promote the proliferation of beneficial bacteria such as lactic acid bacteria and bifid bacterium, while the proliferation of harmful bacteria such as Bacteroidetes and clostridium was effectively inhibited, but had little effect on the number of intestinal microflora. When observing the probiotics index of samples, it was found that catechin, mainly methylated catechin in tea, had a certain regulatory effect on intestinal micro ecology, and the higher its purity, the stronger the effect.

Totally, tea polyphenols play an important role in the establishment of host immune system, resistance to pathogenic microbial infection and inflammation, and the transformation, absorption and metabolism of intestinal substances. Therefore, intestinal flora is closely related to the occurrence and development of a variety of diseases. And how to regulate intestinal flora and promote body health has become a new topic in the field of biomedical science [29]. Tea polyphenols can provide metabolic substrates for intestinal microorganisms and promote the growth and reproduction of intestinal beneficial bacteria. At the same time, its antibacterial activity can inhibit intestinal harmful bacteria to reduce the toxicity of pathogenic bacteria. Therefore, tea polyphenols have the ability to regulate intestinal flora.

4.3.2 Inhibition of oral pathogens

Caries is a common bacterial infectious disease, and Streptococcus mutans is most commonly detected. Studies have shown that oral rinsing with tea polyphenols can significantly reduce bacterial adherence to tooth enamel [30]. The application prospect of tea polyphenols in the prevention and treatment of caries was suggested. In addition, tea polyphenols and EGCG have significant inhibitory effects on halitosis pathogens, suggesting a promising application in oral health care [31].

Tea polyphenols and lemon extract have in vitro antibacterial activity against Streptococcus mutans, and the combined application has an enhanced effect, which can inhibit the adhesion of bacteria on the surface of the glass slide.

Periodontitis is caused by direct damage caused by plaque microorganisms and their stimulating factors and indirect damage caused by immune response to bacterial metabolites.

Tea polyphenols have certain anti-inflammatory and periodontal protective effects. Studies have shown that tea polyphenols and EGCG can increase the integrity of the gingival epithelium, enhance the antibacterial effects of antibiotics such as metronidazole and tetracycline against Porphyromonas gingivalis, and inhibit the ability of bacteria to adhere to the oral epithelium [32].

5. Anti-inflammatory

5.1 Mechanism for anti-inflammatory action

Recent years, some research have found that tea polyphenols are effective at anti-inflammatory, though reducing cytokine production, declining pro-inflammatory factors and other methods to inhibit or reduce inflammation. EGCG, which has been shown to inhibit lipopolysaccharide (LPS) -induced TNF-A production, induces nitric oxide synthase production in mouse macrophages and human keratinocytes or endothelial cells. The potential mechanisms of the anti-inflammatory and anticancer effects of EGCG have been studied. One of the mechanisms of action is to inhibit the activation of NF-KB, which regulates the expression of multiple key genes that are essential for inducing inflammatory cytokines and immune responses and/or fighting apoptosis.

①Inhibition of NF-κB transcriptional activity: The transcriptional activity of NF-κB is closely related to the expression and secretion of many inflammatory factors. Studies have demonstrated that tea polyphenols exert its anti-inflammatory biological effect through the transcriptional activity of effective NF-κB. In mouse peritoneal macrophages and macrophage lines, EGCG can inhibit LPS-activated MAPKp38 signaling pathway, thereby inhibiting IκB degradation and NF-κB activation, and promoting the expression of low IL-12[33].

Some research found that EGCG inhibits IL-1β -induced inflammation by degrading IκB and inhibiting NF-κB activity. In addition, EGCG inhibits TNF- induced inflammatory cytokine IL-8 expression by inhibiting TNF- induced activation of IκB kinase and subsequent activation of IκB/NF-κB signaling pathway, thereby inhibiting cell adhesion to endothelial cells after activation by pro-inflammatory cytokines [34, 35].

②TLRs signal path: It was found that tea polyphenols can effectively inhibit TLRs signaling pathway and exert anti-inflammatory effect. Youn et al. found that EGCG can regulate the downstream MyD88 and TRIF-dependent signaling pathways of TLR, thus inhibiting the subsequent expression of inflammatory target genes. EGCG can also inhibit TLR2 and TLR4 signaling pathways through laminin receptor. For example, EGCG inhibits pgN-induced TLR2 signaling pathway through its receptor, and then inhibits pgN-induced pro-inflammatory introduction factor production and MAPK activation. EGCG inhibits TLR4 signal through laminin receptor, and thus inhibits lPS-induced downstream signal activation [36, 37].

③High mobility group protein 1 (HMBG1): HMBG1 is secreted and released in damaged cells and activates a variety of immune cells to perform a series of inflammatory responses, which is considered to be an effective target of inflammation induced by infection and trauma. In endotoxin-stimulated macrophages, EGCG can effectively stimulate autophagy and reduce cytoplasmic HMGB1 expression level. After LPS lethal dose, EGCG can block HMGB1 release, alleviate LPS - induced end toxemia and reduce mortality. The inhibitory effect of EGCG on HMGB1 may play an important role in the protection of fatal end toxemia and sepsis.

5.2 Anti-inflammatory action

Studies have found that tea polyphenols can effectively inhibit osteoarthritis, especially in the suppression of chronic joint inflammation. Tea polyphenols can effectively inhibit the activity of

multiple enzymes, play an important role in joint inflammation and joint destruction, and related signal transduction, to protect when osteoarthritis occurring and developing.

Serval studies have confirmed that tea polyphenols have a definite inhibitory effect on intestinal inflammation.

Tea polyphenols has a significant inhibitory effect on acute colitis induced by sugar anhydride esters, which depends on the inhibitory effect on inflammatory cytokines [38]. Other studies have also found other effects of tea polyphenols on intestinal inflammation. For example, tea polyphenols can effectively reduce the intestinal toxicity caused by chemotherapeutic drugs, reduce macrophage inflammatory protein-2, myeloperoxidase activity, etc.

Studies have found that tea polyphenols play an important role in cardiovascular inflammation to regulate. Inflammation is an important factor in occurrence and development of cardiovascular diseases such as atherosclerosis. Further research found that tea polyphenols' regulatory effect on inflammation-induced ventricular and vascular remodeling in multiple animal models such as myocardial ischemia and atherosclerosis is related to its regulation of NF-κB and other inflammatory factors [39].

Studies have found that tea polyphenols have a clear protective effect on sepsis. In animal models induced by lipopolysaccharide (LPS), tea polyphenols can effectively block the production of tumor necrosis factor-α (TNF-α) induced by endotoxin, improve the hemodynamic status of animal models of sepsis, and reduce the lethality of endotoxin Rate.

6. Conclusion

According to the researches, tea polyphenols are able to play a significant role in the inhibition of cancer, cardiovascular disease like AD, and immunocompetence.

In terms of inhibiting cancer, three perspectives are discussed in the article, which are inhibition of carcinogenesis, inhibition of proliferation, as well as induction of apoptosis of cancer cells. According to the research, tea polyphenols have practical functions on reducing cancer risk and curing or blocking cancer.

EGCG and catechinic can effectively work on antibiosis and anti-inflammatory, which has been studied a lot. This mentions some relevant information and application above, and gives some discussion, which could help researchers find out useful direction about this area.

Green tea polyphenols, in particular EGCG is able to fulfill neuroprotective effects both in vitro and in vivo study. TF has demonstrated its good anti-oxidative properties, coupled with its abilities to render preformed fibrils into a non-toxic form, dissociate fibrils, modulate cell signaling pathways (Akt), return tau to its unfolded monomeric state, attenuate ant mitochondrial apoptotic pathway. However, since few studies have been performed in humans, more clinical studies are needed in the near future to better understand the mechanisms of TP's neuroprotective properties and the exact doses of TP to prevent AD.

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