Animal Nutrition 6 (2020) 115–123

Contents lists available at ScienceDirect

Animal Nutrition

journal homepage: http://www.keaipublishing.com/en/journals/aninu/

Review Article

Antioxidant mechanism of tea polyphenols and its impact on health benefits

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ARTICLE INFO

Article history:
Received 12 November 2019
Received in revised form
8 January 2020
Accepted 9 January 2020
Available online 23 January 2020

Keywords:
Tea polyphenols
Antioxidant activities
Animal production
Signal transduction pathway

ABSTRACT

Tea trees have a long history of cultivation and utilization. People in many countries have the habit of drinking tea and choosing green tea, oolong tea, or black tea according to different regions and personal tastes. Tea polyphenols are a general term for polyphenol compounds in tea, and has been shown to have good effects on antioxidant, anti-inflammatory, cancer prevention and regulation of lipid metabolism. Tea polyphenols have been widely used as antioxidants in disease treatment and animal husbandry, but their specific mechanism of action needs to be further clarified and revealed. This review focuses on the definition, classification, antioxidant activity and the regulation of signaling pathways of tea polyphenols. This paper also aims to examine the application of tea polyphenols in human and animal health, providing a scientific basis for this application in addition to proposing future directions for the development of this resource.

1. Introduction

Tea is considered as one of 3 major beverages in the world, along with coffee and cocoa. According to historical records, Chinese have been cultivating and using tea trees for more than 3,000 years. Tea is widely accepted as a daily drink in China as well as in many countries. Since ancient times, tea has been used as a health product or medicine to prevent and treat various diseases. Previous studies have shown the numerous benefits of tea, such as antioxidant, bacteriostatic, and anti-cancer activities and regulation of lipid metabolism.

In general, tea can be divided into 3 types on the basis of the level of fermentation: green tea, oolong tea, and black tea (Chan et al., 2011). Polyphenol oxidase contained in the tea is a heat-labile enzyme. The activity of this enzyme is reduced by steam heating during the fermentation, and hence green tea contains more polyphenol compounds (Anandh Babu and Liu, 2008). This also explains why green tea has better antioxidant properties than black tea. Many clinical diseases have been shown to be associated with oxidative damage. Tea polyphenols are an effective antioxidant that can prevent and treat the diseases by scavenging free radicals and regulating the activity of different types of oxidases in the body. This is due to the phenolic hydroxyl structure in which the electrons have a conjugation effect; the hydrogen ion's binding ability is weakened and, therefore, more likely to be dissociated, so the active hydrogen ion neutralizes the free radicals and other reactive oxygen species, scavenging the free radicals (Zuo et al., 2018).

Research has also identified the molecular signaling pathways associated with the antioxidant properties of tea polyphenols;

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Peer review under responsibility of Chinese Association of Animal Science and Veterinary Medicine.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.aninu.2020.01.001

however, many studies have not fully demonstrated the exact mechanism of tea polyphenol bioactivity. In practice, tea polyphenols are becoming popular in livestock and poultry production. However, there have been challenges, e.g., lower bioavailability than vitamin antioxidants, higher prices than alternatives, and decreased palatability of the feed due to the tannins from the polyphenols. The purpose of this paper is to review the physicochemical properties and antioxidant capacity in tea polyphenols research, paying particular attention to the impact on signal transduction pathways.

2. Definition and classification of tea polyphenols

The polyphenolic compounds contained in green tea mainly include flavonoids, flavanols, phenolic acids, and the like. Tea polyphenols, commonly known as catechins, are flavonoid compounds with a basic structure of α-phenyl-benzopyran, which is about 18% to 36% of the dry weight of tea leaves (Khan and Mukhtar, 2007). The most important types of tea polyphenols can be divided into the following 4 types: (−)-epigallocatechin-3-gallate (EGCG), (−)-epicatechin-3-gallate (ECG), (−)- epigallocatechin (EGC) and (−)-epicatechin (EC) (Yang et al., 1999). The catechins are composed of 3 hydrocarbon rings and are structurally classified into ester catechins (EGCG, ECG) and non-ester catechins (EGC, EC). The structure of several major tea polyphenols is shown in Fig. 1. The EGCGmakes up about 59% of total catechins, while EGC accounts for about 19%, ECG accounts for 13.6% and EC accounts for about 6.4% (Ciraj et al., 2001). Sorted by their oxidation resistance: EGCG ≈ ECG > EGC > Gallic acid (GA) > EC = Catechin (Ravindranath et al., 2007; Rice-Evans, 2010). The number and position of hydroxyl groups in the molecular structure of these polyphenolic compounds largely determine their antioxidant properties. As such, the catechins have strong hydrogen supply capacity on the B and C rings, and the 2,3- double bond and the unsaturated 4-oxo group in the C-ring promote the electron delocalization (free electron) of the ortho-dihydroxy catechol in the B-ring (Senanayake, 2013). Furthermore, the antioxidant activity of these polyphenols is related to the molecular structure, starting conditions, and microenvironment of the reaction medium (Zhou et al., 2005; Dai et al., 2008). In addition to tea polyphenols, there are various phenol derivatives and polyphenol analogs in tea, such as quercetin, kaempferol, myricetin. Since these substances all have a 4-oxo 3-hydroxy C ring structure, they exhibit oxidation resistance (Xing et al., 2019).

At the cellular level, EGCG appears to be the most biologically active substance in polyphenols (Lorenz, 2013). Under normal temperature conditions, industrially produced tea polyphenols exhibit different colors due to the different carriers, usually yellow or light green powder. Tea polyphenols are sensitive to pH, and the properties are stable under low pH conditions; however, strong acid, strong alkali, strong light irradiation and high temperatures easily cause deterioration. EGCG is water-soluble but insoluble in organic solvents and partially soluble in grease (Zeng et al., 2017).

3. Antioxidant and anti-oxidative stress activity of tea polyphenols

Free radicals are highly active molecules produced during cellular respiration and normal metabolism, and reactive oxygen species (ROS) are closely related to physiological and pathological processes in animals. The species mainly include superoxide anion free radicals (O_2^-), hydroxyl free radicals (OH^-), hydrogen peroxide (H_2O_2), and others (Bergamini et al., 2004; Kim et al., 2009). At low levels, ROS can function as signaling molecules that regulate cellular basic activities, such as cell growth and cellular adaptive responses (Hazel and Roebuck, 2001). When the balance between the accumulation of ROS and the body's antioxidant process is broken, it causes oxidative stress and damage to cells and tissues, causing vari ous diseases (Mao et al., 2017). There is clear evidence that free radicals are associated with the development of diseases, such as atherosclerosis, emphysema, and cancer (Hayashi and Iguchi, 2010). Table 1 summarizes the antioxidant effects of tea polyphenols and their associated potential mechanisms.

In vivo experiments have shown that tea polyphenols can increase levels of rat serum catalase (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD), and can reduce the production of malondialdehyde (MDA). These findings reveal that tea polyphenols regulate the oxidoreductase system, improve the body's anti-oxidation ability (Ahmed et al., 2017; Negishi et al., 2004), and prevents oxidative stress caused by bacterial infections and intestinal damage (Zhang et al., 2019). In addition, tea polyphenols can restore the levels of serum total protein, tumor necrosis factor-α (TNF-α), and caspase-3 in the liver of rats with hepatotoxicity induced by azathioprine (El-Beshbishy et al., 2011). This indicates that tea polyphenols protect against liver injury in rats through antioxidant, anti-inflammatory, and antiapoptotic mechanisms. The content of ECG, EGC and EC in tea is relatively low, and there have been few reports on the use as a feed additive in animals.

In vitro experiments have shown that EGCG exhibits cancer-preventing activity by inhibiting the accumulation of ROS in the body, and EGCG can accelerate programmed cell death by blocking DNA synthesis in cancer cells without harming normal cells (Chen et al., 2001). Stimulation of the primary hepatocytes of goats with EGCG was shown to promote cell proliferation, improve cell membrane integrity, and facilitate cell survival and function under oxidative stress (Zhong, 2013). EGCG, ECG, EGC, EC all have the function of inhibiting the proliferation of human colon cancer cells HCT-116 and SW-480, but the effect of egcg is the best, which is mainly related to its content (Du et al., 2012). In the cell signaling pathway, EGCG regulates apoptosis induced by oxidative stress via the protein kinase B (Akt) and c-Jun N-terminal kinase (JNK) signaling pathways. ECG up-regulates mitogen-activated protein kinase (MAPK), antioxidant response element (ARE) gene expression, thereby enhancing the ability of the cell's antioxidant defense system (Nie et al., 2002). Furthermore, the key cellular pathways for the body's antioxidants are nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-kappa B (NF-κB), and so on (Jiang et al., 2017).

In addition, a therapeutic effect has been shown with the combination of tea polyphenols and other drugs. Tea polyphenol with taurine can reduce the level of lipopolysaccharides in rats and can protect the liver, providing a new method for treating nonalcoholic steatohepatitis (Zhu et al., 2017). Likewise, tea polyphenol with Trolox can inhibit gene mutations, base detachment, and DNA strand breaks that are caused by excessive oxygen free radicals; these synergistic effects have an activity sequence of EC = ECG > EGCG > EGC (Wei et al., 2006).

4. Antioxidant mechanisms of green tea polyphenols

A growing number of epidemiological studies have shown that the intake of polyphenols delays aging and helps prevent and treat cancer and neurodegenerative, cardiovascular, and cerebrovascular diseases (Kumar and Xu, 2017). After entering the animal body, the mechanism by which tea polyphenols produce antioxidant effects includes the following processes: the increase in activity of antioxidant enzymes, the inhibition of lipid peroxidation, the scavenging of free radicals in synergy with other nutrients (Nakagawa

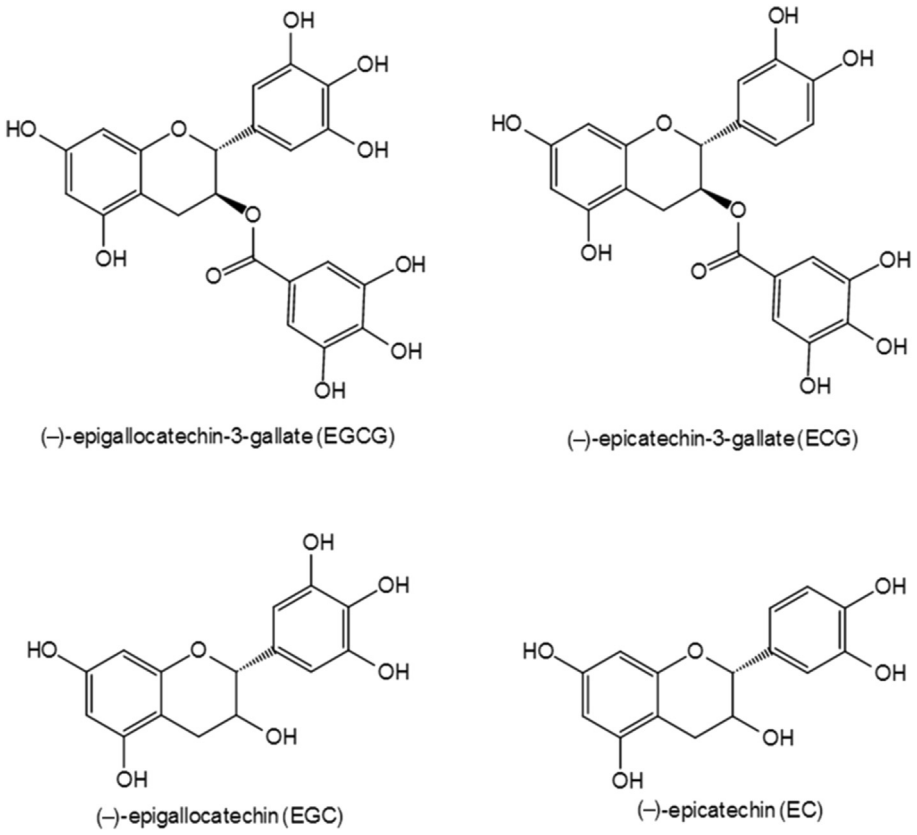

Fig. 1. Structures of the major tea polyphenols.

Table 1
The antioxidant effects of tea polyphenols and their associated potential mechanisms.

Experiment material	Compound	Observed effects	Reference
Electromagnetic radiation-exposed rats	EGCG	↑CAT; ↑SOD; ↑GSH-Px; ↓MDA	Ahmed et al. (2017)
Spontaneously hypertensive rats	Tea polyphenols	↑CAT; ↓Blood pressure	Negishi et al. (2004)
Hepatotoxicity of azathioprine-induced rats	Tea polyphenols	↑CAT; ↑GSH-Px; ↑Restoring serum total protein, TNF-α and caspase-3 levels in the liver	El-Beshbishy et al. (2011)
Salmonella typhimurium infection C57BL/6 male mice	Tea polyphenols	↑CAT; ↑SOD; ↓Oxidative stress occurring in the process of ileal injury induced by*Salmonella typhimurium*	Zhang et al. (2019)
Primary hepatocytes of goat	Tea polyphenols	↑Cell proliferation; ↑Cell membrane integrity; ↑Antioxidase	Zhong (2013)
Human colon cancer cell line (Colo-205)	Tea polyphenols	↓Lipid peroxidation	Jiang et al. (2017)
6-hydroxydopamine-induced apoptosis in PC12 cells	ECG	↑MAPK; ↑ARE gene expression	Nie et al. (2002)
Human colon cancer cell HCT-116 and SW-480	EGCG, ECG, EGC, EC	↓Cell proliferation; ↓Oxidative stress	Du et al. (2012)
Nonalcoholic steatohepatitis rats	Tea polyphenols + taurine	↑Liver antioxidant activity; ↓ROS; ↓LPS	Zhu et al. (2017)
pBR322 plasmid DNA	Tea polyphenols + trolox	Inhibition of DNA oxidative damage	Wei et al. (2006)

EGCG = (−)-epigallocatechin-3-gallate; CAT = catalase; SOD = superoxide dismutase; GSH-Px = glutathione peroxidase; MDA = malondialdehyde; TNF-α = tumor necrosis factor-α; ECG = (−)-epicatechin-3-gallate; MAPK = mitogen-activated protein kinase; ARE = antioxidant response element; EGC = (−)-epigallocatechin; EC = (−)-epicatechin; ROS = reactive oxygen species; LPS = lipopolysaccharides.

and Yokozawa, 2002), and the reduction of oxidation via chelation of metal ions (Yiannakopoulou, 2013). These processes are combined to reflect the effect of antioxidants. The antioxidant mechanism of phenolic compounds can be summarized as a transfer based on hydrogen atoms or a single electron transfer through protons (Rong, 2012); however, catechins and theaflavins may also promote the production of ROS in the body (Lambert and Elias, 2010).

4.1. Direct action on free radicals

ROS is involved in a variety of physiological and pathological processes, mainly in cell signaling conduction, proliferation, differentiation, and apoptosis. Significant accumulation of ROS causes inflammation and neurodegenerative diseases (Cai et al., 2002). Tea polyphenols react with ROS to form relatively stable phenolic oxygen radicals, thus eliminating free radicals. The π-

electron on the benzene ring in the tea polyphenol structure has a conjugation effect on the single electron on the oxygen atom of the phenolic hydroxyl group. The single electron tends to the benzene ring, thereby reducing the activity of the hydrogen-oxygen bond in the phenolic hydroxyl group. The hydrogen activity on the phenolic hydroxyl group increases and the free radicals compete for active oxygen, terminating the auto-oxidation reaction of the free radicals. The metabolites of tea polyphenols also have a certain degree of antioxidant capacity (Almajano et al., 2008; Vuong et al., 2011); however, due to the structural differences in catechins, there is a difference in the elimination of free radicals. In general, the ability of tea polyphenols to scavenge ROS depends on the number of hydroxyl groups in the structure, the environment, and the stability of the phenolic oxygen radicals (Zhao et al., 2001).

4.2. Indirect action on free radicals

In addition to directly scavenging free radicals, tea polyphenols also protect the body from oxidative damage by regulating different types of oxidase and antioxidant enzyme activities. Tea polyphenols can inhibit xanthine oxidase (Rashidinejad et al., 2016), Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Zuo et al., 2014), lipoxidase, cyclic oxidase (Frei and Higdon, 2003; Htay et al., 2008), and can impede activity to reduce the production of oxygen free radicals. In addition, tea polyphenols regulate the expression of certain antioxidant enzymes, such as SOD, glutathione S-transferase (GST), GSH-Px and the like (Yang et al., 2011), to alleviate the structural and functional damage caused by oxidative damage in mitochondria (Yang et al., 2011). Glutathione (GSH) is a reducing substrate for GSH-Px in the process of scavenging H_2O_2. Glutathione reductase (GR) is a key enzyme that reduces glutathione from an oxidized state to a reduced state. The glutamyl cysteine synthetase is the rate-limiting enzyme in the synthesis of glutathione (Chen et al., 2004; Masella et al., 2005). EGCG and ECG can increase the activity of these 2 enzymes and ensure that GSH-Px continuously scavenges oxygen free radicals.

4.3. Complexation of metal ions

Some of the transition metal elements catalyze certain oxidation reactions in the body and generate a large number of free radicals. Calcium is one such element; Ca^{2+} promotes the production of xanthine oxidase. Tea polyphenols inhibit the occurrence of this process by chelating Ca^{2+} (Guo et al., 2005). Iron also catalyzes oxidation; however, the catechol structure in tea polyphenols can chelate Fe^{2+}. Inhibition of iron-induced synaptosome lipid peroxidation showed that different compounds has different inhibitory effects on lipid peroxidation, and different compounds inhibitory effects are in the order EGCG > ECG > EGC > EC, but EGC is the most effective in scavenging lipid free radicals, because compared with EGC, other types of catechins (EGCG, ECG and EC) are more likely to form creams with lipids in the acidic environment of the stomach, reducing their utilization efficiency (Fang et al., 2019; Bernatoniene and Kopustinskiene, 2018). Due to the different positions of compounds involved in the antioxidant activity, the stability of the semiquinone radicals generated during the dehydrogenation reaction also becomes an important factor affecting the antioxidant effect (Guo, 1996).

4.4. Synergistic effect of tea polyphenols and vitamins

Humans and animals require vitamins to maintain normal physiological functions. Vitamins play an important role in body growth, metabolism, and development. Tea polyphenols have been shown to increase the concentration of vitamin E in low-density lipoprotein (LDL) in cholesterol-fed rats and to increase serum antioxidant capacity. Further, the atherosclerosis index showed a dose-dependent improvement with increasing levels of tea polyphenols (Yokozawa et al., 2002). Through the study of total hydrogen peroxide production during the linoleic acid peroxidation process, it was found that the antioxidant effect of tea polyphenols (EGCG, 10 μmol/L) is better than that of α-tocopherol (vitamin E, 10 μmol/L) or ascorbic acid (vitamin C, 10 μmol/L), but the mixture of EGCG, vitamin E, and vitamin C possesses remarkably enhanced antioxidative efficacy when compared to the use of these 3 antioxidants individually (Dai et al., 2008).

5. Effect on signal transduction pathway

When the ability to generate and eliminate free radicals in the body cannot reach equilibrium, oxidative stress can cause damage to the body. Various extracellular stimuli complete the signal transfer through the signaling pathway, and the animal's response to the stimuli is also achieved through the signaling pathway. Tea polyphenols can protect cells from oxidative damage by regulating certain cell signaling pathways. In addition, tea polyphenols are protective against inflammation (Kyung-Joo et al., 2016), cardiovascular diseases (Potenza et al., 2007), cancer (Fujiki et al., 2015), and obesity (Louise et al., 2009); moreover, they regulate lipid metabolism (Kim et al., 2013). The regulatory effect of tea polyphenols on major cellular pathways related to antioxidant activity is shown in Fig. 2.

5.1. Nrf2-Keap1-ARE

Nrf2 is an important redox-sensitive transcription factor, a major regulator of certain antioxidant enzymes and detoxification genes, and it plays an important role in the body's maintenance of redox homeostasis (Jaramillo and Zhang, 2013). Kelch-like ECH-associated protein-1 (Keap1) is an inhibitor of Nrf2. Under normal physiological conditions, keap1 is at a relatively low level when binding to Nrf2. Keap1 is a substrate for ubiquitin E3 ligase (cul3) and can promote the degradation of Nrf2 by proteases. When the cells are subjected to oxidative stress, the Nrf2-Keap1 complex is dissociated, and the undegraded Nrf2 is transferred from the cytoplasm into the nucleus. The Nrf2 promoter binds to the small musculoaponeurotic fibrosarcoma (Maf) protein to form a heterodimer and binds to ARE to promote expression of certain antioxidant enzyme genes (Heiss et al., 2013). Oxidative stress and conditions stimulated by many exogenous chemicals may alter the reduced state of the cysteine residue of Keap1 and cause translocation of Nrf2. When Cys151 is oxidized or covalently modified, Nrf2 ubiquitination can be reduced and separated from the Nrf2-Keap1 complex (Kobayashi and Yamamoto, 2006).

Antioxidant factors regulated by Nrf2 include quinone oxidoreductase 1 (NQO1), heme Oxygenase-1 (HO-1), SOD, CAT, and the like (Vries et al., 2008). Nrf2-mediated HO-1 expression regulates the activity of P38 MAPK and extracellular-signal-regulated kinase (ERK)1/2 signaling pathways, links Nrf2 to the MAPK signaling pathway, and reduces ROS production in animals. It alleviates the oxidative damage of cells and organs caused by ROS and exerts preventive and therapeutic effects in other conditions such as neurodegenerative diseases (Kerio et al., 2013).

Black tea polyphenols can increase the expression of antioxidant enzymes, such as NQO1 and GST in the liver and lung of mice through the Nrf2-ARE pathway. The main pathways for activation of Nrf2 are protein kinase C (PKC) and Pi3 kinase (Pi3-K), but the main pathways of EGCG are Pi3-K/Akt and MAPK. Studies have proven that different tea polyphenols have different ways of

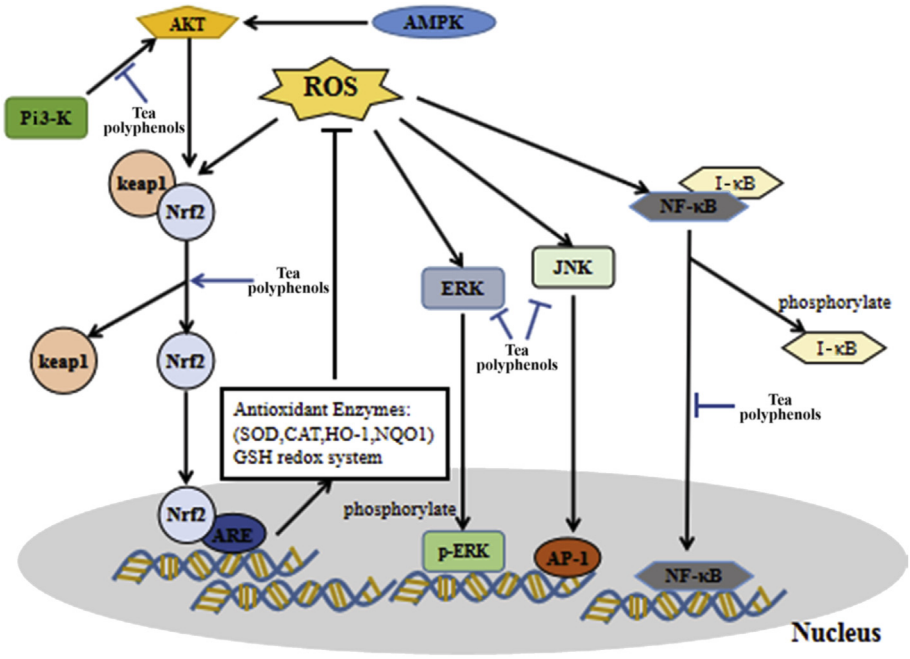

Fig. 2. This schematic illustrates the cellular pathways regulated by tea polyphenols during their antioxidant activity. AKT = protein kinase B; AMPK = adenosine 5'-monophosphate; Pi3-K = Pi3 kinase; ROS = reactive oxygen species; keap1 = Kelch-like ECH-associated protein-1; Nrf2 = nuclear factor erythroid 2-related factor 2; ERK = extracellular-signal-regulated kinase; JNK = c-Jun N-terminal kinase; NF-κB = nuclear factor-kappa B; I-κB = inhibitory protein inhibitor of NF-κB; SOD = superoxide dismutase; CAT = catalase; HO-1 = heme oxygenase-1; NQO1 = quinone oxidoreductase 1; GSH = glutathione; ARE = antioxidant response element; p-ERK = phosphorylated ERK; AP-1 = activating protein-1.

activating Nrf2 (Patel and Maru, 2008). Studies have also shown that mice can change their normal routine when light is provided irregularly. It was found that the expression of the circadian clock gene Bmal1 was decreased, resulting in a decrease in the expression level of the antioxidant gene regulated by the Nrf2 pathway, causing oxidative stress and hepatic lesions. EGCG can improve this condition and increase the expression level of enzymes, such as HO-1 and NQO1, by activating the Nfr2 oxidative defense pathway in the liver and HepG2 cells (Qi et al., 2017). The HO-1 has a function of increasing the antioxidant capacity of cells and NQO1 can reduce the production of cellular ROS (Vasiliou et al., 2006). The protective effect of tea polyphenols against oxidative stress in the animal body was demonstrated.

5.2. NF-κB

NF-κB is an important transcription factor whose primary function is to regulate the expression of anti-apoptotic genes and activate certain proinflammatory cytokine and chemokines (Iliopoulos et al., 2009). Under normal conditions, NF-κB binds to the inhibitory protein inhibitor of NF-κB (I-κB) in the cytoplasm. Under conditions of oxidative stress and excessive ROS accumulation, I-κB rapidly phosphorylates and releases NF-κB to transfer it into the nucleus. At the molecular level, NF-κB is closely related to the occurrence and development of diseases, such as inflammation and organ damage (Potoyan et al., 2015; Nanji et al., 2003). Excessive oxygen free radicals cause activation of NF-κB and regulate the expression of inflammation and immune-related genes, exacerbating apoptosis of vascular smooth muscle cells and causing inflammatory responses (Mitjans et al., 2011). Damage to biofilms by oxygen free radicals can cause vascular endothelial dysfunction in animals, leading to cardiovascular diseases, such as atherosclerosis (Nagle et al., 2006).

Overexpression of I-κB in cells can significantly inhibit NF-κB and increase the activation of ARE and NQO1 genes, indicating that I-κB can increase Nrf2 activity while negatively regulating NF-κB.Inhibitor of NF-κB kinase (IKK) plays a key role in the phosphorylation of I-κB and activation of NF-κB. Inhibitor of NF-κB kinase activity was evaluated by studying tea polyphenols for phosphorylation levels of I-κB-GST fusion protein of mouse fetal epithelial cell line (IEC-6). The results showed that tea polyphenols could induce a decrease in IKK and NF-κB activities, and EGCG had the best inhibitory effect on IKK, which improved the body's antioxidant capacity (Yang et al., 2001). Studies have shown that during activation of the NF-κB pathway, many proteins negatively regulate the Nrf2 pathway, and that the P65 protein has a significant inhibitory effect on Nrf2. This mechanism is the direct interaction between P65 protein and Nrf2 inhibitor Keap1 protein. Tea polyphenol pretreatment significantly reduced the expression of P65 protein in rats, thereby inhibiting the activation of NF-κB and restoring the activities of antioxidant enzymes, such as SOD, CAT, and GSH-Px; the rats were protected from renal ischemia-reperfusion injury (RIRI) (Li et al., 2014).

5.3. MAPK

The MAPK pathway-associated signal is a family of highly conserved protein kinases whose basic component is a tertiary kinase pattern, including Mitogen-Activated Protein Kinase Kinase Kinase (MKKK), Map Kinase Kinase (MKK), and MAPK (Takahashi et al., 2010). Activation of this system has important regulatory effects on cell growth, differentiation, and response to stress. A large number of studies have found that there are 3 pathways involved in MAPK, namely the ERK signaling pathway (Sturm et al., 2010), JNK pathway, and the p38 MAPK signaling pathway (Wagner and Nebreda, 2009; Bradham and Mcclay, 2006).

There is a close relationship between oxidative stress and MAPK. The massive accumulation of ROS can cause oxidation of intracellular proteins and lipid peroxidation of cell membranes, leading to cell damage and tissue necrosis (Tunc et al., 2009). This may be due

to ROS that activate ERK/p38 and cause oxidative damage to neurons (Wang et al., 2011). Tests have shown that oral administration of EGCG to mice can reduce antibody levels in their own serum and protect cells from the toxic effects of TNF-α. The molecular mechanism of this protection is the specific phosphorylation of p38 MAPK, which leads to reduced viability (Hsu et al., 2007). In addition, the oxidative stress model of HepG2 cells was constructed by using low-concentration H_2O_2 to explore the therapeutic effect of EGCG. The phosphorylation of p38 MAPK by EGCG increased the content of intracellular CAT and enhanced the stability of CAT mRNA (Murakami et al., 2002).

6. Application of tea polyphenols in animal models

Tea polyphenols are found in medical practice and scientific research as a good antioxidant with good free radical scavenging effects in response to oxidative stress. Since oxidative stress is closely related to the occurrence and development of many chronic diseases in humans. Tea polyphenols was documented to prevent and treat various diseases (Wang et al., 2008). Cancer is a chronic disease that poses a huge threat to the health of the people. In China, these diseases often occur due to the aging of the population and unhealthy lifestyles (He, 2018). The production and accumulation of MDA increases the risk of cancer in humans. In the primary stage of cancer, lipid peroxide-induced DNA mutations are increased by the accumulation of MDA (Nair et al., 2007). The levels of adducts produced by MDA and DNA in breast cancer patients are significantly higher than those in healthy individuals. Studies have shown that matrix metalloproteinases (MMP) are involved in the pathogenesis of breast cancer. EGCG inhibits the development of disease by mediating the epigenetic induction of MMP-3 and inhibiting the activity of MMP-2 and MMP-9 in breast cancer cells (Limaye, 2015). A rat colon cancer model was induced with azomethane (AOM) to investigate the therapeutic effects of tea polyphenols on human colon cancer. The number of aberrant crypt foci (ACF) and its extent by AOM were significantly decreased after feeding rats with 0.24% of composite polyphenols containing 65% EGCG for 8 wk. The expression levels of β-catenin and cyclin D1 were decreased and ACF cell apoptosis was increased (Xiao et al., 2008). Tea polyphenols have also been shown to prevent respiratory cancers, digestive cancers, and urinary cancers caused by different pathogenic factors in animal models. In addition to antioxidant properties, tea polyphenols also prevent mutations in genetic material, regulate detoxification enzyme activity, and inhibit tumorigenesis in the process of preventing cancer (Ahmad and Mukhtar, 1999).

Cardiovascular and cerebrovascular diseases are collectively referred to as ischemic or hemorrhagic diseases of the heart, brain and systemic tissues caused by hyperlipidemia, atherosclerosis, and hypertension. It is more common among the middle-aged and elderly people over the age of 50. The number of people who die of cardiovascular and cerebrovascular diseases every year in the world is as high as 15 million, ranking first in all causes of death. The rat model of cardiac hypertrophy was established by abdominal aortic constriction (AC). The MDA content in the rat heart was gradually increased and the antioxidant enzyme activity was decreased. EGCG has the ability to inhibit telomere shortening and loss of telomere repeat-binding factor 2 (TRF2) in cardiac cells to reduce apoptosis of cardiomyocytes (Sheng et al., 2013). Oral EGCG can cause significant increase in antioxidant enzyme activity in rats with isoproterenol-induced myocardial infarction, and lipid peroxidation is inhibited to ensure the integrity of myocardial cell membrane and reduce the incidence of myocardial infarction (Devika and Prince, 2008). With the deepening of lipoprotein research, it is found that the level of low-density lipoprotein cholesterol (LDL-C) is positively correlated with the occurrence of atherosclerosis. Tea polyphenols have multiple phenolic hydroxyl groups to inhibit the oxidation of cholesterol. Inhibition of deposition of lipids on the walls of blood vessels. On the other hand, the oxidation of unsaturated fatty acids is prevented, thereby reducing the content of cholesterol in the serum and maintaining the dynamic balance of the normal entry and exit of lipids in the arterial wall, and has an anti-atherosclerotic effect.

Gut microbiota balances nutrient acquisition and energy regulation by processing the indigestible components of our daily diet (Consortium, 2012). There are more than 1,000 different types of bacteria and microorganisms in the human digestive system, and the composition of the microbial ecosystem in the body plays a vital role in human health. When the microbial composition is altered, it will induce or trigger the production of certain diseases (Yano et al., 2015). The metabolism and absorption of dietary polyphenols by the human body mainly depend on the biotransformation of microorganisms in the intestine. Some polyphenols enter the colon and are converted into small molecule compounds under the action of bacterial enzymes and microorganisms, and the other part enters the hepatic and intestinal circulation to exert physiological functions (Duynhoven et al., 2011). The synergistic use of 4% green tea powder and Lactobacillus plantarum can significantly increase the microbial diversity in the intestinal tract of C57BL/6J mice and selectively reduce the number of harmful bacteria (Axling et al., 2012). The mechanism of tea polyphenols in improving intestinal microbial composition mainly focuses on tea polyphenols providing metabolic substrates for beneficial bacteria such as bifidobacteria and lactic acid bacteria, and its antibacterial activity can affect the cell membrane function and energy metabolism of harmful bacteria, inhibits the growth of Bacteroides and Pachybacteria (Marchesi et al., 2016). Short-chain fatty acids (SCFA) are the major metabolites produced by bacteria that ferment dietary fiber in the gastrointestinal tract, various studies have confirmed its regulatory effect on metabolic syndromes (Yin et al., 2018). Tea polyphenols can produce SCFA by intestinal fermentation. Increasing SCFA production can achieve the purpose of acidifying the intestinal environment, in order to promote the absorption of nutrients, especially minerals, and inhibit the growth of pathogenic bacteria (Sun et al., 2018). Tea polyphenols can show better effects in Improving intestinal function, indicating that the bioactive components in tea are digested and absorbed in the intestinal tract of animals. However, studies have shown that only 0.1% of EGCG will be bioavailable after entering the body (Zhibin et al., 2018), and it can be seen that the bioavailability of tea polyphenols is very low. The reason for the conjecture may be related to the rapid metabolism of polyphenols and poor intestinal transport capacity (Neilson et al., 2007). Although the bioavailability of animals to tea polyphenols is low, higher levels of tea polyphenols still cause toxicity to the body. Feeding high doses (1%) of tea polyphenols in colitis mice can cause symptoms of nephrotoxicity and affect liver and kidney function, causing oxidative damage in the body. The same results were obtained in experiments in healthy mice. However, using low-dose (0.01% or 0.1%) tea polyphenols to feed colitis mice, it was found that tea polyphenols showed protective effects on liver and kidney and other organs (Murakami, 2014). Therefore, the optimal use of tea polyphenols in the prevention and treatment of different diseases needs to be confirmed.

At present, in addition to being a health care drug, tea polyphenols are widely used as a safe feed additive in livestock and poultry farming. In the production of pigs, it can improve animal production performance and immunity, reduce the body's lipid oxidation level, protect cell structure and functional integrity, and prevent organ damage and animal diseases caused by lipid

peroxidation (Xing et al., 2019). Currently, lipid oxidation has been recognized as the main deteriorating mode of frozen meat (Jamilah et al., 2009). Proteins are degraded by oxidation, causing impaired protein function and loss of nutritional value (Promeyrat et al., 2013; Utrera and Mario, 2013). Tea polyphenols also has the effect of prolonging the storage time of meat products and improving the quality of meat. Piglets were injected with diquat to establish an oxidative stress model. After 7 d of dietary supplementation with tea polyphenols, it was found that immune damage and growth inhibition caused by oxidative stress were alleviated and improved, and T lymphocyte proliferation and activation were promoted (Deng et al., 2010). Studies have shown that tea polyphenols help to increase the number of beneficial bacteria in the intestines of pigs, reduce the number of Clostridium, and reduce the amount of feces and ammonia. In this way, the control of nitrogen-containing substances with animal excrement is important for environmental protection and the promotion of healthy farming (Hara et al., 1995). Green tea extract has anti-avian adenovirus type 4 (fadv4) (Aslam, 2014) and anti-avian influenza (H5N2) (Taechowisan et al., 2018) effect during poultry farming and is superior to catechins such as EGCG, EGC and ECG. As antibiotics are banned worldwide, finding good antibiotic substitutes is an important direction for the healthy development of animal husbandry. Studies have shown that broilers fed diets containing 0.5% to 2% tea polyphenols can improve growth performance, muscle antioxidant capacity and meat quality, and the effect is better than diet supplemented with 0.1% oxytetracycline calcium (Rahman et al., 2018). It has been proved that tea polyphenols have the potential to replace antibiotics. Studying the effect of tea polyphenols on egg quality showed that under the premise of lowering the cholesterol content of egg yolk and improving the fatty acid composition, the antioxidant level of eggs was increased and the storage time of eggs was prolonged (Uuganbayar et al., 2005). However, there have also been reports that feeding tea to egg poultry will reduce egg weight and eggshell quality, mainly because the tea contains the anti-nutritional factor tannin (Kara et al., 2016). Therefore, in the further development and utilization of such resources, we should pay attention to solve this problem and explore the optimal use of tea.

7. Perspectives

A large number of animal experiments and human clinical applications have proven that tea polyphenols have anti-oxidation, anti-cancer, anti-obesity, anti-allergic and other biological functions. Tea polyphenols are used in the prevention and treatment of neurodegenerative diseases, cardiovascular and cerebrovascular diseases, cancer, diabetes, high blood pressure, scurvy and other diseases. Tea polyphenols exert anti-oxidation activity mainly by regulating Nrf2 signaling pathway, and also stimulate NF-κB and MAPK pathways. However, the specific mechanism by which tea polyphenols exhibit good biological functions in the body has not been fully elucidated, and further tests are needed to verify whether high-dose tea polyphenols are bio-toxic to humans and animals.

Conflicts of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

Acknowledgement

This study was financially supported by the National Key R & D Program (2018YFD0500405), the National Nature Science Foundation of China (31972582), the Science and Technology Projects of Changsha City (kq1801059), the STS regional key projects of Chinese Academy of Sciences (KFJ-STS-QYZD-052), the Youth Innovation Team Project of ISA, CAS (2017QNCXTD_ZCS), and the Earmarked Fund for China Agriculture Research System (CARS-35).

We thank Editage [http://www.editage.cn] for English language editing.

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