Food Sci Biotechnol (2022) 31(8):957–970
https://doi.org/10.1007/s10068-022-01069-0

REVIEW

The roles of catechins in regulation of systemic inflammation

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Received: 24 January 2022 / Revised: 11 March 2022 / Accepted: 14 March 2022 / Published online: 24 March 2022
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Abstract Catechins are a phytochemical present in plants such as tea leaves, beans, black grapes, cherries, and cacao, and have various physiological activities. It is reported that catechins have a health improvement effect and ameliorating effect against various diseases. In addition, antioxidant activity, liver damage prevention, cholesterol lowering effect, and anti-obesity activity were confirmed through in vivo animal and clinical studies. Although most diseases are reported as ones mediating various inflammations, the mechanism for improving inflammation remains unclear. Therefore, the current review article evaluates the physiological activity and various pharmacological actions of catechins and conclude by confirming an improvement effect on the inflammatory response.

Keywords Catechins · Epigallocatechin gallate · Inflammation · Anti-inflammatory effect · NF-κB pathway

Introduction

Inflammation is a defense mechanism to protect the organs from external injury and infection (Lomax and Calder, 2009). The immune system increases the expression of immune cells and many other inflammatory mediators in response to changes that lead to tissue damage. However, the inflammatory response caused by excessive stimulation becomes chronic, contributing to the promotion and progression of disease in various tissues (Ferrucci and Fabbri, 2018). An immediate reaction to a microbial or virus infection can cause acute inflammation, while a slow and sustained response results in chronic inflammation (Krishnamoorthy and Honn, 2006). These inflammatory responses affect the whole body through blood and lymphatic vessels and exacerbate the onset and symptoms of various diseases (Schwager and Detmar, 2019). The increase in the chronic and systemic inflammatory response is known to be a hallmark of diseases such as cancer, diabetes, cardiotoxicity, metabolic syndrome, and respiratory disorders (Coussens and Werb, 2002; Halaris, 2013; Lontchi-Yimagou et al., 2013; Racanelli et al., 2018). Thus, it is very important to control the inflammatory response.

The inflammatory response appears as an interaction of various signaling pathways such as toll-like receptor (TLR) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) with an increase in the content of nitric oxide (NO), inflammatory cytokines and chemokines (Kobayashi, 2010). When external pathogens such as lipopolysaccharide (LPS), lipopeptides, heavy metals and microbial or virus infections enter the body, they react with various TLRs in the cellular membrane to stimulate a signal in the cell (Bazzoni et al., 1991; Sochocka et al., 2019). The stimulation of TLRs activates Toll/IL-1 receptor (TIR) domain-containing adaptors, such as myeloid differentiation primary response 88 (MyD88), Toll/interleukin-1 receptor domain-containing adapter protein (TIRAP), and TIR-domain-containing adapter-inducing interferon-β (TRIF) (Piao et al., 2013). This activation continuously recruits the expression of IL-1 receptor-associated kinase-4 (IRAK-4), leading to activation of

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NF-κB, signal transducer and activator of transcription 1 (STAT1), activator protein 1 (AP-1), and mitogen-activated protein kinase (MAPK) containing c-Jun N-terminal kinases (JNK), p38 MAPK and extracellular signal-regulated kinase (ERK) (Li et al., 2002). Increased NF-κB, STAT1, and AP-1 enters the nucleus, and these proteins increase the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Lee et al., 2017). This downstream signaling ultimately inhibits the antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and stimulates the secretion of inflammatory cytokines and chemokines (Schulze-Osthoff et al., 1997) (Fig. 1). Therefore, to effectively eliminate the inflammatory reaction and prevent from various diseases, research on various natural products and compounds is being conducted (Keservani et al., 2010). In particular, the physiological activities of catechin, one of the phenolic compounds, are being continuously studied. However, a schematic pathway of the bioactivity of catechins is insufficient, and this paper was designed to effectively understand the contents.

Catechins

Catechins containing various isoforms are polyphenol compounds belonging to the flavonoid family and are present in various fruits and leaves of plants (Crespy et al., 2004). In general, catechins are not essential for human nutrition, but they can help prevent various diseases and improve health (Arts et al., 2001). Catechins are composed of two steric forms of (+)-catechin and its enantiomer, including the compounds such as epigallocatechin gallate (EGCG), epigallocatechin (EGC), and epicatechin gallate (ECG) (Fig. 2) (Tsuchiya, 2001). Catechin structure is composed of two or more aromatic A ring similar to resorcinol and B ring similar to catechol, each containing at least one aromatic hydroxyl connected by a carbon bridge and a dihydropyran heterocycle (C ring) having a hydroxyl group. The structure of C ring does not have double bond unlike flavonoid structure. EC and EGC are the epimer of a catechin containing 2 or 3 hydroxyl groups in the B ring and a hydroxyl group in the C-ring. ECG and EGCG are ester derivatives of EC and EGC, respectively, and have a structure bonding with gallate at the hydroxyl position of the C ring (Botten et al., 2015; Musial et al., 2020). These catechins are distributed in various plants including green tea, apples, persimmons, beans, peaches, black grapes, and berries, and various beverages such as cider and red wine

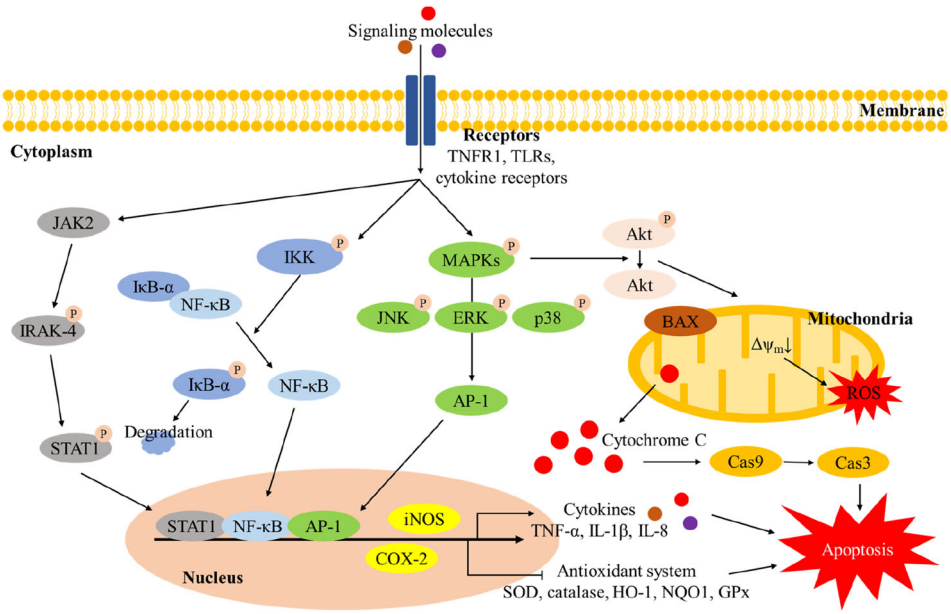

Fig. 1 A schematic pathway of inflammatory biomarkers regulated by catechins and their derivates in cell. *TNFR1* TNF-α receptor 1, *TLRs* toll-like receptors, *JAK2* Janus kinase 2, *IRAK-4* IL-1 receptor-associated kinase-4, *STAT1* Signal transducer and activator of transcription 1, *IκB-α* nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *IKK* IκB kinase, *MAPK* mitogen-activated protein kinase, *JNK* c-Jun N-terminal kinases, *ERK* extracellular signal-regulated kinase, *AP-1* activator protein 1, *Akt* protein kinase B, *BAX* BCL2 Associated X, *ROS* reactive oxygen species, *Cas9* caspase-9, *Cas3* caspase-3, *iNOS* inducible nitric oxide synthase, *COX-2* cyclooxygenase-2, *TNF-α* tumor necrosis factor-α, *IL-1β* interleukin-1β, *IL-8* interleukin-8, *SOD* superoxide dismutase, *HO-1* heme oxygenase-1, *NQO1* NAD(P)H quinone oxidoreductase 1, *GPx* glutathione peroxidase

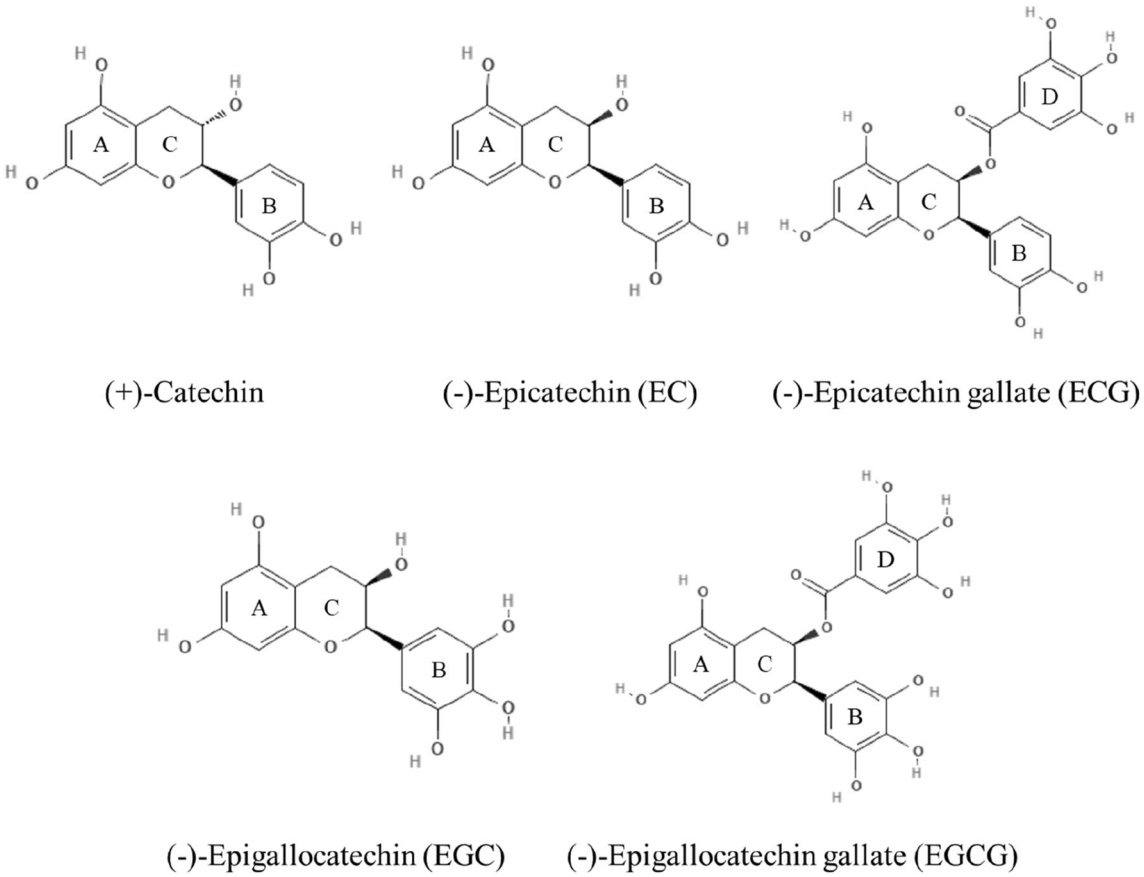

Fig. 2 Chemical structures of catechins. Available from: https://pubchem.ncbi.nlm.nih.gov

(Andersen et al., 2005; Gadkari and Balaraman, 2015; Santos-Buelga and Scalbert, 2000). Catechins are reported to have excellent antioxidant activity, antibacterial activity, and anti-diabetic effect (Iacopini et al., 2008; Kajiya et al., 2004; Kim et al., 2021). Catechins effectively scavenge oxidative stress and free radicals by binding proteins, lipids, nucleic acids and metals in tissues (Yang et al., 2014). These physiological activities are mainly caused by the presence of at least 5 hydroxyl groups included in the structure of the content of diphenylpropanoid skeleton ($C_6C_3C_6$) of catechins, and these structural characteristics affect the antioxidant ability of catechins (Gadkari and Balaraman, 2015). In particular, catechins showed considerable antioxidant activities compared to glutathione (GSH), vitamin C and other flavonoids, which means that catechins might be functional material in ameliorating human health and improving cellular redox homeostasis (Grzesik et al., 2018).

Interest in the intake of various bioactive substances is increasing (Keservani et al., 2010). In particular, demand for the intake of catechins, which have considerable physiological activities, is continuously increasing. To reduce the inflammatory response caused by various diseases, the mechanism related to the anti-inflammatory effect of catechins with various physiological activities will be analyzed and presented.

Alzheimer's disease and inflammation

Alzheimer's disease (AD) is a typical neurodegenerative disease that includes continuous loss of memory and cognitive function (Kumar and Singh, 2015). Although the pathogenesis of AD has not been precisely elucidated, it is believed that various causes, such as the microglia-induced inflammatory response, oxidative stress, and neuroinflammation, affect the pathogenesis of AD (Kása et al., 1997; Martini et al., 2019; Selkoe, 1991; Tian et al., 2007). Especially, inflammatory cytokines such as TNF-α and interleukins activate the phosphorylation of MAPKs such as JNK, ERK and p38 (Lee et al., 2017). These phosphorylated kinases simulate the expression of NF-κB and STAT1 and reduced the activation of Akt (Patel et al., 2017). The inhibition of Akt activation induces apoptosis cascade, hyperphosphorylation of tau protein, amyloid beta (Aβ) plaque formation, and damage to the cholinergic system (Ksiezak-Reding et al., 2003; Petry et al., 2020; Zhang et al., 2015). In addition, these dysfunctions in brain

Table 1 Physiological studies of catechins on Alzheimer's disease

Materials	Doses[a]	Species/organ (origin)[b]	Stressors[c]	Biomarkers[d]	References
EGCG	15 mg/kg (p.o.)	SAMP8 mice/FC, HIP	AD-transgenic	↑Synaptophysin, PSD95 ↓p-tau, $A\beta_{1-42}$, BACE-1	Guo et al. (2017)
EGCG	2 μM/well	BV-2 cells/ Microglia	LPS	↓TLR4, nitric oxide, iNOS, TNF-α, IL-1β	Park and Chun (2016)
EGCG	5 mg/kg/day (i.p.)	SD rats/HIP	Scopolamine	↑AChE, SOD, LTP ↓MDA	Kim et al. (2022)
EGCG	50 mg/kg (p.o.)	APP/PS1 mice/WB	AD-transgenic	↑IL-10, IL-13 ↓IL-1β	Bao et al. (2020)
Catechin hydrate	50 mg/kg (p.o.)	Wistar rats/HIP, CC	Streptozotocin	↑GSH, GPx, GR, catalase ↓AChE, TNF-α, IL-1β	Ahmed et al. (2013)
Green tea catechins	40 mg/kg of b.w. (p.o.)	BALB/c mice/HIP	$PM_{2.5}$	↑SOD, GSH, BCl-2, AChR-3α, ChAT ↓p-JNK, p-IκB-α, TNF-α, BAX, Aβ, p-tau, AChE	Kim et al. (2021)
Green tea catechins	50 mg/kg of b.w. (p.o.)	C57BL/6 mice/WB, HIP, CC	HFD	↑p-Akt, BDNF, IDE ↓p-JNK, p-tau, Aβ, COX-2, IL-1β	Kim et al. (2020b)
Persimmon catechin	20 mg/kg of b.w. (p.o.)	ICR mice/WB	Trimethyltin chloride	↑SOD, GSH, MMP, ATP, p-Akt ↓AChE, p-JNK, p-tau, cytochrome c, IRS-1pSer, TNF-α, p-NF-κB, BAX	Kim et al. (2018)

[a]Maximal dose of referred study. Body weight (b.w.)

[b]Abbreviation of organs. *FC* frontal cortex, *HIP* hippocampus, *WB* whole brain, *CC* cerebral cortex

[c]Abbreviation of stressors. *AD* Alzheimer's disease, *LPS* lipopolysaccharide, *PM* particulate matter, *HFD* high-fat diet

[d]Abbreviation of biomarkers. *PSD95* postsynaptic density protein 95, *Aβ* amyloid beta, *BACE-1* beta-secretase 1, *TLR4* toll-like receptor 4, *iNOS* inducible nitric oxide synthase, *TNF-α* tumor necrosis factor-α, *IL* interleukin, *AChE* acetylcholinesterase, *SOD* superoxide dismutase, *LPT* ling term potential, *MDA* malondialdehyde, *GSH* glutathione, *GPx* glutathione peroxidase, *GR* glutathione reductase, *BCl-2* B-cell lymphoma 2, *AChR-3α* acetylcholine receptor α3, *ChAT* choline acyltransferase, *p-JNK* phosphorylated c-Jun N-terminal kinases, *p-IκB-α* phosphor-nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, *BAX* BCl-2 associated X, *BDNF* brain derived neurotrophic factor, *IDE* insulin degrading enzyme, *COX-2* cyclooxygenase-2, *MMP* mitochondrial membrane potential, *IRS-1pSer* phosphorylated insulin receptor substrate 1 (Ser), *p-NF-κB* phosphorylated nuclear factor kappa-light-chain-enhancer of activated B cells

tissue continuously stimulate the chronic inflammatory cascade resulting in the death of neuronal cells and dysfunction in cortical and hippocampal tissues, and ultimately initiates cognitive deficit, memory loss, abnormal behavior, and AD (Kumar and Singh, 2015; Tsai et al., 2019).

Most catechins are decomposed into (+)-catechin or (+)-epicatechin and gallic acid by intestinal microorganisms in the small intestine and are decomposed to various colonic microbial ring-fission metabolites in the large intestine and absorbed into the blood (Zhu et al., 2015). The catechins and these metabolites can cross brain tissue through the blood–brain barrier (BBB), and this suggests that catechins and their metabolites might play an important role in suppressing neurodegenerative diseases (Unno et al., 2017). Although compounds with various physiological activities in development show excellent bioactivity in eliminating inflammation, their utility as pharmaceuticals or health functional foods is less because they do not pass through the BBB (Shlosberg et al., 2010). On the other hand, catechins not only have excellent physiological activity, but can also easily pass through the BBB and affect brain neurons (Unno et al., 2017).

Intake of green tea catechins improved cholinergic dysfunction by regulating acetylcholine (ACh) content and acetylcholinesterase (AChE) activity in hippocampal tissue (Kim et al., 2021). In addition, it was reported that green tea catechins have an effect on cognitive function improvement by increasing ACh content and choline acyltransferase (ChAT) expression and inhibiting AChE activity in high-fat diet (HFD)-induced diabetic cognitive impairment mice (Kim et al., 2020b). In particular, EGCG suppressed recognition and memory dysfunction and synaptic damage by regulating synaptophysin and postsynaptic density protein 95 (PSD 95) in the frontal cortex and the hippocampus (Guo et al., 2017). ACh mainly plays a role in suppressing the expression of NF-κB in immune cells and macrophages, which inhibits the synthesis of pro-inflammatory cytokines and exhibits anti-inflammatory activity (Shenhar-Tsarfaty et al., 2014). Thus, inhibition of AChE and butyrylcholinesterase (BChE) by catechins might reduce the inflammatory response by inhibiting the

Table 2 Physiological studies of catechins on metabolic disease related to high fat diet

Materials	Doses[a]	Species/organ (origin)	Stressors[b]	Biomarkers[c]	References
EGCG	50 μM/well	QSG-7701 cells /Human liver cell	OA	↑SOD, catalase, GPx, LC3A/B, Beclin-1, p-ERK ↓P62, p-JNK, p-p38	Wu et al. (2021)
EGCG (Physiological studies of catechins)	50 mg/kg/day	C57BL/6 J/liver	HFD	↓Triglyceride, total cholesterol, ALT, AST, NEFA	Wu et al.
EGCG	0.7 g/day/kg of b.w. (p.o.)	Wistar rats (female)/plasma, fecal	Semisynthetic diet high in cholesterol and fat	↑HDLC ↓Total cholesterol, Triglyceride, free fatty acids, total lipid, cholesterol, fat	Raederstorff et al. (2003)
Epicatechin	200 mg/kg (p.o.)	C57BL/6 J/adipose tissue	HFD	↓TNF-α, IL-6, Saa3, Ip-10, Ccl19, cd11c, Cidea	Sano et al. (2017)
(+)-Catechin	300 μmol/L	3T3-L1 cells/ adipocytes	IBMX, DEX	↑cAMP, PKA, ATGL, PLIN ↓C/EBPβ, C/EBPδ, PPARγ, SREBP1C	Jiang et al. (2019)
Green tea catechin	1.7 mg/day (p.o.)	C57BL/6 J/plasma	ApoE-deficient transgenic mice	↑HDLC ↓Total cholesterol, Triglyceride, VLDLC, MDA	Miura et al. (2001)
Green tea catechin	0.1% (w/v) (p.o.)	Lewis rats (female)/liver	Haemorrhage/ resuscitation	↓ALT, IL-6, PMNL, ICAM-1, p-IκB-α, CAE	Relja et al. (2011)
Green tea catechin	50 mg/kg (p.o.)	C57BL/6/liver, adipose	HFD	↓TNF-α, IL-1β, TNFR1, p-IRS-1, p-JNK, iNOS, COX-2, HMGCR, PPARγ, FAS	Kim et al. (2020b)
Wine grape seed flour catechin	5% (w/v) (p.o.)	C57BL/6 J/plasma	HFD, HFrD	↑HDLC ↓Triglyceride, Total cholesterol	Seo et al. (2020)

[a]Maximal dose of referred study. Body weight (b.w.)

[b]Abbreviation of stressors. *OA* oleic acid, *HFD* high-fat diet, *IBMX* isobutylmethylxanthine, *DEX* dexamethasone, *HFrD* high-fructose diet

[c]Abbreviation of biomarkers. *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *p-ERK* phosphorylated extracellular signal-regulated kinase, *p-JNK* phosphorylated c-Jun N-terminal kinases, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *NEFA* non-esterified fatty acids, *HDLC* high-density lipoprotein cholesterol, *TNF-α* tumor necrosis factor-α, *IL* interleukin, *Saa3* serum amyloid A3, *Ip-10*C-X-C motif chemokine ligand 10, *C–C motif* chemokine, *Ccl19* ligand 19, *cd11c* integrin αX subunit, *Cidea* cell death-inducing DNA fragmentation factor alpha-like effector A, *cAMP* cyclic adenosine monophosphate, *PKA* protein kinase A, *ATGL* adipose triglyceride lipase, *PLIN* perilipins, *C/EBPβ* CCAAT-enhancer-binding protein β, *C/EBPδ* CCAAT-enhancer-binding protein δ, *PPARγ* peroxisome proliferator activated receptor gamma, *SREBP1C* sterol regulatory element-binding protein 1C, *VLDLC* very-low-density lipoprotein cholesterol, *MDA* malondialdehyde, *PMNL* polymorphonuclear leukocyte, *ICAM-1* intercellular adhesion molecule-1, *p-IκB-α* phosphor-nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, *CAE* chloroacetate esterase, *TNFR1*TNF-α receptor 1, *p-IRS-1* phosphorylated insulin receptor substrate-1, *iNOS* inducible nitric oxide synthase, *COX-2* cyclooxygenase-2, *HMGCR* 3-hydroxy-3-methylglutaryl-CoA reductase, *FAS* fatty acid synthase

degradation of ACh (Bertrand and Wallace, 2020). Chronic inflammation stimulates the production of tumor necrosis factor-α (TNF-α). Increased TNF-α is combined with TNF-α receptor (TNFR) and stimulates inflammatory response (Cheng et al., 2014). This signaling activates the phosphorylation of JNK, which is related to the initiation of apoptosis cascade, increasing caspase activation. An increase in apoptosis signaling causes neuronal inflammation and cell death (Li et al., 2018). However, administration of catechin and EGCG suppressed TNF-α release in primary glial cells, and expression of TLR4 in LPS-induced microglial BV-2 cells (Angeloni et al., 2012; Park and Chun, 2016). Persimmons, which are rich in catechins, suppressed mitochondrial damage by regulating mitochondrial function and apoptotic expression such as B-cell lymphoma 2 (Bcl-2), Bcl-2 associated X protein (BAX), and cytochrome C in Aβ-induced mice (Kim et al., 2018; Lee et al., 2012). Kim et al. (2022) reported that EGCG improved cognitive dysfunction through an ameliorating effect against scopolamine-induced long-term potentiation (LTP) blockade of the CA1 region in the hippocampal tissue of SD mice. Administration of green tea rich in catechins inhibited tau and inflammatory signaling by suppressing the expression of p-JNK, phosphorylated protein kinase B p-(Akt) and p-tau, and stimulated the Aβ clearance pathway by regulating brain-derived neurotrophic factor (BDNF), insulin-degrading enzyme (IDE), and Aβ in HFD-induced diabetic mice

Table 3 Physiological studies of catechins on hepatic disease

Materials	Doses[a]	Species/organ (origin)	Stressors[b]	Biomarkers[c]	References
EGCG	6 g/kg/day	Wistar rats/liver	Ethanol	↑Glycogen, ADH, ALDH, GST ↓AST, ALT, GGT, LDH, cytochrome P450, bilirubin	Anuradha and Kaviarasan (2007)
Epicatechins	300 mg/kg (p.o.)	Sprague Dawley rats/liver	CCl_4	↓α-SMA, TGF-β, p-ERK1/2, p-Smad1, TNF-α, MMP2, MMP9, IL-17	Wang et al. (2018)
(+)-Catechin	16 μg/mL/well	Huh-7 cells/human hepatoma cells	HCV	↓COX-2, p-NF-κB, NS5A-Myc	Lee et al. (2011)
Green tea catechin	0.1% (w/v) (p.o.)	Sprague Dawley rats/Liver	BDL	↓ALT, procollagen-α1(I), AP-1, α-SMA, 4-HNE, TGF-β1, TNF-α	Zhong et al. (2003)
Green tea catechin	50 mg/kg/day (p.o.)	Wistar rats/liver	Sanfenon	↓AST, ALT, 4-HNE, 8-OHdG, AP-1, TGF-β1, α-SMA	Kobayashi et al. (2010)
Green tea catechin	10% (w/v) (p.o.)	Hamsters/liver	CCl_4	↑GSH, ADH, cytochrome P450 reductase, HDLC ↓MDA, total cholesterol, triglyceride, LDLC. p53	Elgawish et al. (2015)
Black tea catechin	2% (w/v) (p.o.)	Sprague Dawley rats/liver	Aflatoxin	↑SOD, catalase, GST, GR, GPx ↓AST, ALT, ALP	Alm-Eldeen et al. (2015)

[a]Maximal dose of referred study. Body weight (b.w.)

[b]Abbreviation of stressors. *CCl_4* carbon tetrachloride, *HCV* hepatitis C virus, *BDL* bile duct ligation

[c]Abbreviation of biomarkers. *ADH* alcohol dehydrogenase, *ALDH* aldehyde dehydrogenase, *GST* glutathione S-transferase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma glutamyl peptidase, *LDH* lactate dehydrogenase, *α-SMA* α-smooth muscle actin, *TGF-β* transforming growth factor-β, *p-ERK1/2* phosphorylated extracellular signal-regulated kinase ½, *TNF-α* tumor necrosis factor-α, *MMP2* matrix metalloproteinase-2, *MMP9* matrix metalloproteinase-9, *IL-17* interleukin-17, *COX-2* cyclooxygenase-2, *p-NF-κB* phosphorylated nuclear factor kappa-light-chain-enhancer of activated B cells, *NS5A-Myc* nonstructural protein 5A-Myc, *AP-1* activator protein 1, *4-HNE* 4-hydroxynonenal, *8-OHdG* 8-hydroxy-2′-deoxyguanosine, *GSH* glutathione, *HDLC* high-density lipoprotein cholesterol, *MDA* malondialdehyde, *LDLC* low-density lipoprotein cholesterol, *SOD* superoxide dismutase, *GR* glutathione reductase, *GPx* glutathione peroxidase, *ALP* alkaline phosphatase

(Kim et al., 2020b). Finally, the mechanism between Alzheimer's disease and inflammatory effect of catechins were presented in Table 1.

Metabolic syndrome and inflammation

Metabolic syndrome is a disorder involving various diseases including glucose tolerance, obesity, dyslipidemia, and hypertension, and increases the incidence of cardiovascular disease, type 2 diabetes, and cancer (Kaur, 2014). In general, excessive intake of high fat and high sugar is the main cause of metabolic syndrome, and when these contents increase in the blood, lipid accumulation in the liver and adipose tissue is accelerated through dyslipidemia (Kumar et al., 2014). Non-alcoholic fatty liver disease (NAFLD) from the intake of HFD increases inflammatory cytokines by activating the TNF-a/receptor-interacting protein kinase 3 (RIPK3) axis (Xu et al., 2019). In addition, various saturated fatty acids and lipids stimulate the signaling of TLR by binding the fatty acid parts of ligands (Raetz, 1990). The activation of TLR increases the secretion of inflammatory cytokines such as TNF-α and interleukins by upregulating NF-κB and apoptotic pathways and increasing protein expression of TLR-mediated protein and gene signaling (Doğanyiğit et al., 2020). In particular, lipid accumulation in hepatic tissue stimulates the activation of immune cells that secrete inflammatory cytokines such as TNF-α and interleukin 1 beta (IL-1β), thereby stimulating gluconeogenesis and glycogenolysis, and it initiates insulin resistance and early diabetic symptoms through an increase in blood glucose (King, 2008; Ramnanan et al., 2010). Increased glucose and cytokines in serum abnormally phosphorylate the residue of insulin receptor substrate-1 (IRS-1) that regulates insulin signaling (Alipourfard et al., 2019). Phosphorylated IRS-1 increases cytokines by downregulating the expression level of Akt and accelerating apoptosis signaling and the NF-κB pathway in various organs such as the liver, heart, lung, brain, and kidney, and adipose tissues (Hussain et al., 2012; Zand et al., 2017).

However, intake of powdered green tea, which is rich in catechins, reduced inflammatory cytokines such as IL-1β and TNF-α in adipose and hepatic tissues, and regulated lipid and cholesterol accumulation metabolism in HFD-induced C57BL/6 mice (Kim et al., 2020a, 2020b). Catechin-rich wine grape seed flour inhibited adipose tissue

Table 4 Physiological studies of catechins on respiratory disease

Materials	Doses[a]	Species/organ (origin)	Stressors[b]	Biomarkers[c]	References
EGCG	200 mg/kg (p.o.)	Sprague Dawley rats/ lung	Hg, Cd, Cr, Ni, Cu	↑Excretion of heavy metals ↓Bilirubin, ALT, AST	Wang et al. (2020)
Epicatechin	500 μM/well	MRC-5 cells/human lung fibroblast cells	Amiodarone	↑Mitochondrial complex I, ATP, SOD, catalase ↓MDA, PC, nitric oxide	Santos et al. (2017)
Catechin hydrate	40 mg/kg of b. w. (p.o.)	Swiss albino mice/lung	Benzo(a)pyrene	↑GPx, GST, GR, GSH, catalase, SOD, QR, BCl-2, ↓LPO, LDH, CYPOR, mEH, NF-κB, IL-6, TNF-α, COX-2, p53, BAX, Caspase-3	Shahid et al. (2016)
Catechin	100 μg/mL/ well	A549 cells/pulmonary carcinoma	Influenza A (H1N1) virus	↓Neuraminidase activity, plaque formation	You et al. (2018)
Catechin	500 μM/well	MRC-5 cells/human lung fibroblast cells	Amiodarone	↑Mitochondrial complex I, ATP, SOD, catalase ↓MDA, PC, nitric oxide	Santos et al. (2017)
Green tea catechins	10 μg/mL/well	A549 cells/pulmonary carcinoma	$PM_{2.5}$	↑SOD, BCl-2 ↓ROS, apoptosis, MDA, caspase-3, BAX	Zhang et al. (2018)
Green tea catechins	40 mg/kg of b.w. (p.o.)	BALB/c mice/lung	$PM_{2.5}$	↑SOD, GSH ↓MDA, TNF-α, p-JNK, p-IκB-α, p-NF-κB, BAX, caspase-1, COX-2, IL-1β	Kim et al. (2021)

[a]Maximal dose of referred study. Body weight (b.w.)

[b]Abbreviation of stressors. *PM* particulate matter

[c]Abbreviation of biomarkers. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *SOD* superoxide dismutase, *MDA* malonaldehyde, *PC* protein carbonyl groups, *GPx* glutathione peroxidase, *GST* glutathione-S-transferase, *GR* glutathione reductase, *GSH* glutathione, *QR* quinone reductase, *BCl-2* B-cell lymphoma 2, *LPO* lipid peroxidation, *LDH* lactate dehydrogenase, *CYPOR* crystal structure of a NADPH-cytochrome P450, *mEH* microsomal epoxide hydrolase, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-α, *COX-2* cyclooxygenase-2, *BAX* BCl-2 associated X, *PC* protein carbonyl groups, *ROS* reactive oxygen species, *p-JNK* phosphorylated c-Jun N-terminal kinases, *p-IκB-α* phosphor-nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, *BAX* BCl-2 associated X, *IL-1β* interleukin-1β

weight, and plasma lipid concentration in high fructose diet-induced mice (Seo et al., 2020). (+)-Catechin treatment inhibited the lipid degradation of adipocytes by reducing the expression of CCAAT-enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ) and regulating the cAMP/protein kinase A (PKA) signaling pathway in 3T3-L1 cells (Jiang et al., 2019). According to Raederstorff et al. (2003), the intake of EGCG has been reported to decrease the absorption of triglycerides and cholesterol. Catechins also help to excrete cholesterol and fat from the body, thereby lowering LDL cholesterol in the blood (Miura et al., 2001). EGCG inhibited the expression of monocyte chemoattractant protein-1 (MCP-1) and activation of NF-κB against TNF-α-induced human umbilical vein endothelial cells (HUVEC) (Relja et al., 2011). Finally, the mechanism between metabolic syndrome and inflammatory effect of catechins were presented in Table 2.

Hepatic diseases and inflammation

Inflammation is the cause of diseases such as viral, alcoholic, fatty and autoimmune chronic liver dysfunction, which affects all stages of liver disease (Czaja, 2014). A prolonged inflammatory response affects the onset of liver fibrosis, cirrhosis, fatty liver, and cancer, and inhibits the detoxification of various toxins generated in the body, reducing the ability to maintain health in the body (Seki and Schwabe, 2015). Hepatic tissue damaged by chronic inflammation promotes apoptosis and activates hepatic stellate cells and Kupffer cells (Friedman et al., 2008). These cells induce inflammation and hepatic fibrosis, and also induce the transformation of hepatic stellate cells into myofibroblasts through the activation of transforming growth factor beta 1 (TGFβ1), and endothelial growth factor (Friedman and Arthur, 1989). This transformation produces inflammatory cytokines and chemokines, and increases the expression of antigens on T lymphocytes and natural killer T cells. Eventually, the chronic immune response leads to apoptosis and fibrosis (Uhal et al., 2007). In addition, activated Kupffer cells continuously stimulate inflammatory response by inducing the production of reactive oxygen stress (ROS) and NO, which causes DNA damage, apoptosis, and promotion of pro-inflammatory genes (Canbay et al., 2003).

Administration of green tea catechins suppressed hepatic fibrosis by reducing the expression of activator protein 1 (AP-1), α-smooth muscle actin (α-SMA), TGF-β1, 4-hydroxynonenal (4-HNE), and 8-hydroxy-2′-

Table 5 Physiological studies of catechins on gastrointestinal disease

Materials	Doses[a]	Species/organ (origin)	Stressors[b]	Biomarkers[c]	References
EGCG	100 mg/kg (i.g.)	CF-1 mice/Plasma	Non-stressor	↑SGLT-1 ↓α-Amylase activity, GLUTs	Forester et al. (2012)
EGCG	1.5 mM (p.o.)	C57BL/6 mice (female)/colon	DSS	↑Bowel length, SOD, GPx ↓MPO, MDA,	Brückner et al. (2012)
EGCG	0.3% (w/w) (p.o.)	C57BL/6 mice/colon, ileum	HFD	↑claudin-1, occludin, ZO-1, JAMA, HIF-1α ↓TNF-α, calprotectin	Dey et al. (2020)
EGCG	0.05% (w/w) (p.o.)	ICR mice/colon	DSS	↑HO-1, p-ERK 1/2 ↓p-PI3K, p-IκB-α, iNOS, COX-2, IL-6, IL-1β, TNF-α, p-p65, nitric oxide	Chiou et al. (2012)
Epicatechin	300 mg/kg (p.o.)	C57BL/6 J mice/colon	DSS	↑SOD, GPx, catalase ↓TNF-α, IL-6, nitric oxide, MPO, NF-κB, MDA	Zhang et al. (2016)
Cocoa catechin	500 mg/kg (p.o.)	Balb/C mice (female)/colon	DSS	↑Bowel length, ↓MPO, IL-6, nitric oxide, COX-2, pSTAT3, pSTAT1α, IL-1β, TNF-α, IFNγ	Andújar et al. (2011)
Green tea catechin	2% (w/w) (p.o.)	C57BL/6 J mice/Jejunal, ileal, colon	HFD	↓TNF-α, iNOS, MCP-1, CD14, MD2, TLR4	Dey et al. (2019)
Green tea catechin	2% (w/w) (p.o.)	C57BL/6 mice/colon, ileum	HFD	↑Claudin-1, occludin, ZO-1, JAMA, HIF-1α ↓TNF-α, calprotectin	Dey et al. (2020)

[a]Maximal dose of referred study. Body weight (b.w.)

[b]Abbreviation of Stressors. *DSS* dextran sulfate sodium, *HFD* high-fat diet

[c]Abbreviation of biomarkers. *SGLT-1* sodium-glucose transport-1, *GLUT* glucose transporter, *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *MPO* myeloperoxidase, *MDA* malondialdehyde, *ZO-1* zonula occludens-1, *JAMA* junctional adhesion molecule A, *HIF-1α* hypoxia-inducible factor 1-alpha, *TNF-α* tumor necrosis factor-α, *HO-1* heme oxygenase-1, *p-ERK1/2* phosphorylated extracellular signal-regulated kinase 1/2, *p-PI3K* phosphorylated phosphatidylinositol 4,5-bisphosphate, *p-IκB-α* phosphor-nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, *iNOS* inducible nitric oxide synthase, *COX-2* cyclooxygenase-2, *IL-6* interleukin-6, *IL-1β* interleukin-1β, *pSTAT3* phosphorylated signal transducer and activator of transcription 3, *pSTAT1α* phosphorylated signal transducer and activator of transcription 1α, *IFNγ* interferon gamma, *MCP-1* monocyte chemoattractant protein-1, *CD14* cluster of differentiation-14, *MD2* myeloid differentiation factor 2, *TLR4* toll-like receptor 4

deoxyguanosine (8-OHdG) and inhibited oxidative stress by regulating the activation of stellate cells (Kobayashi et al., 2010). Catechins such as ECG, EGC and EGCG protected against liver fibrosis by inhibiting the expression of TGF-β and phosphorylation of ERK1/2 and Smad1/2 in CCl_4-induced fibrotic rat (Wang et al., 2018). Green tea catechins also decreased the expression of procollagen-α1(I) and α-SMA, and inhibited pro-inflammatory cytokines, growth factor-β modification and accumulation of 4-HNE. This regulation resulted in the inhibition of liver fibrosis and bile duct adhesion-dependent changes by preventing the activation of astrocytes in the liver (Zhong et al., 2003). (+)-Catechin inhibited cirrhosis caused by chronic hepatitis C virus (HCV) infection by inhibiting HCV replication and inflammatory protein expression of COX-2 and NF-κB (Lee et al., 2011). Finally, the mechanism between hepatic diseases and inflammatory effect of catechins were presented in Table 3.

Respiratory disease and inflammation

Pulmonary inflammation is caused by the inhalation or invasion of external contaminants. Sources of external pollutants mainly include tobacco smoke, toxins, bacteria, viruses, and particulates including heavy metals (Adler and Li, 2001). The inflammatory response caused by cigarette smoke leads to chronic obstructive pulmonary disease (COPD), and air pollution containing particulate matter (PM), heavy metal, biomass fuels, carbon dioxide and ozone induce idiopathic pulmonary fibrosis (Johannson et al., 2014; Polosa et al., 2016). In addition, it has been reported that various pulmonary viruses such as influenza virus, respiratory syncytial virus (RSV), adenovirus, and coronavirus respond easily to the respiratory tract, and stimulate the inflammatory response of lung tissue, causing various symptoms such as tonsillitis, bronchitis, and pneumonia (Lessler et al., 2009). This viral lung injury causes secondary bacterial pneumonia, and inflammatory cytokines produced in the lung tissue have effects throughout the whole body (Conti et al., 2020). Lung tissue

is involved in the expression of inflammation by interacting with various cells, including epithelial cells and immune cells surrounding the airways and alveoli. Airway epithelial cells secrete mucus to trap particles in the inhaled air as a physical system that repels external toxicants (Knudsen and Ochs, 2018). To suppress pulmonary damage by inducers, antimicrobial peptides, proteases, cytokines and chemokines are secreted in pulmonary epithelial cells (Wong et al., 2016). However, excessive chronic inflammation stimulates macrophages to secrete inflammatory mediators and various enzymes and increases the number of lymphocytes, resulting in the destruction of the alveoli (Ingersoll et al., 2011).

PM continuously increases toxicity in respiratory organs (Huang et al., 2017). Intake of green tea catechins ameliorated $PM_{2.5}$-induced systemic inflammation in BALB/c mice by suppressing the deficits of the antioxidant system and mitochondrial function, and regulating the expression of TNF-α, p-JNK, p-NF-κB and IL-1β (Kim et al., 2021). PM contains heavy metals, carbon monoxide and polycyclic aromatic hydrocarbons (PAHs) (Shou et al., 2019). Administration of catechins hydrate modulated benzo(a)-pyrene-induced apoptotic toxicity and inflammation by regulating the expression of TNF-α, NF-κB, COX-2, BAX and caspase-3 in mice lung tissue (Shahid et al., 2016). Wang et al. (2020) reported that EGCG helps the excretion of various heavy metals, including Hg, Cd, Cr, Ni, and Cu, absorbed into the body and reduces toxicity in tissues. Catechins have a high binding affinity with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins containing 3-chymotrypsin-like cysteine protease (3CL), RNA-dependent RNA polymerase (RdRp), and receptor-binding domain (RBD), so they have the potential to act as an excellent multi-targeting agent to regulate COVID-19 pandemic. (Mishra et al., 2021). In addition, catechins in green tea, coffee, and berries also act as a potent inhibitor of influenza A virus, preventing infection (Kaihatsu et al., 2014; Onishi et al., 2020; Sekizawa et al., 2013; You et al., 2018). Catechin and epicatechin inhibited damage of mitochondrial complex I, reduced ATP level, and NO production in amiodarone-induced human lung fibroblasts (Santos et al., 2017). Finally, the mechanism between respiratory disease and inflammatory effect of catechins were presented in Table 4.

Gastrointestinal (GI) tract and inflammation

Inflammatory bowel disease (IBD) is a chronic immune disease of unknown etiology related to the uncontrolled mucosal immune response of the intestinal microflora in the host intestine (Takaishi et al., 2008). IBD damages tight junction (TJ) proteins, resulting in altered intestinal permeability and impaired epithelial barrier function, and increased immune response due to changes in intestinal flora (Lee, 2015). Alterations in the gut microbiota are responsible for influencing various diseases such as obesity, irritable bowel syndrome, tropical enteropathy, antibiotic-associated diarrhea, and vaginitis, and impair the digestion and absorption of nutrients, energy homeostasis, and maintenance of intestinal tissue of the host (Musso et al., 2010; Qin, 2002). Changes in the gut microbiota increase the inflammatory response by stimulating cytokine signaling pathways and indicate intestinal imbalances through changes in some microbial-derived metabolites such as short-chain fatty acids (SCFAs) (Huda-Faujan et al., 2010). Immune response eventually indicates damage to the intestinal tissue, causing nutritional abnormalities and an increase in inflammatory response (Musso et al., 2010). Symptoms of IBD are reported as Crohn's disease (CD) and ulcerative colitis (UC), and the immune pathology of IBD appears to be due to the overexpression of interferon-γ (IFN-γ) and TNF-α (Rafa et al., 2010). When the epithelial barrier is destroyed by an increase in the inflammatory response or infection of pathogenic bacteria, dendritic cells and macrophages are activated to react with antigens and present antigens to the surface through major histocompatibility complex (MHC) class II complexes (Bedford et al., 2006; Kelsall et al., 2005). This response promotes the differentiation of naive T cells into effector and regulatory T cells, and ultimately increases cytokines (Leon et al., 2006).

Catechins can regulate intestinal microbial balance by modulating components of intestinal metabolites. Catechins absorbed through the intestinal tract exhibit various physiological activities, but unabsorbed catechin also plays an important role in the intestine (Forester et al., 2012; Shabbir et al., 2021; Stalmach et al., 2010). This is reported to play the role of prebiotics by stimulating the growth of symbiotic bacteria such as *Lactobacillus plantarum* using phenolic compounds as substrates and perturbing the function of the cytoplasmic membrane of gram-negative pathogenic bacteria such as *Stenotrophomonas maltophila* (Liu et al., 2018; Taylor et al., 2005). Inflammation causes an imbalance of the *Firmicutes* and *Bacteroidetes* (F/B) ratio, leading to several pathologies including obesity, diabetes and IBD (Stojanov et al., 2020), whereas intake of catechins also increases microbial metabolic functions related to SCFAs biosynthesis by regulating the F/B ratio (Xue et al., 2016). In addition, catechin metabolites such as phenylvalerolactones, valerolactones, and phenylvaleric acids digested in the intestine promote the production of SCFAs by anaerobic fermentation to help improve intestinal health (Santangelo et al., 2019). EGCG reduced gut-derived endotoxin translocation and inhibited the loss of TJ proteins such as claudin-1, occludin, zonula

occludens-1 (ZO1) and hypoxia-inducible factor 1-alpha (HIF-1α) in HFD-induced diabetic mice (Dey et al., 2020). In addition, catechins reduce the inflammatory response by regulating the expression of NF-κB, MAPK, and nuclear factor erythroid-2-related factor 2 (Nrf2) in the intestine and the infiltration and proliferation of immune-related cells including neutrophils, macrophages, and T lymphocytes (Fan et al., 2017; Brückner et al., 2012). Finally, the mechanism between gastrointestinal (GI) tract and inflammatory effect of catechins were presented in Table 5.

Safety concern of catechins

It is generally considered that safe for ingestion of low-dose catechins or green tea preparations that contain large amounts of catechins (Church et al., 2015; Lee et al., 2002; Mazzanti et al., 2015). In particular, administration of catechins has been reported to have a protective effect on liver tissue in various hepatic toxicity disease models such as HFD, carbon tetrachloride, acetaminophen, and D-galactosamine (Kim et al., 2020b; Liu et al., 2015; Park et al., 2015; Yao et al., 2015). However, recent studies have reported hepatic toxicity by intake of dietary supplements containing high doses of catechins or green tea. In a rodent model, ingestion of high concentration catechins increased serum alanine aminotransferase (ALT) and bilirubin content, and caused gastrointestinal (GI) tract toxicity (Galati et al., 2006; Isbrucker et al., 2006; Lambert et al., 2010). It has also been reported that administration of EGCG (500 mg/kg, i.g.) presented in liver and GI toxicity in beagle dogs (Isbrucker et al., 2006). According to Mazzanti et al. (2015), it was reported that intake of green tea containing high doses of catechins increased hepatotoxicity by increasing periportal and portal vein inflammation in patients. Although the numerous studies related to hepatic toxicity of high doses of catechins are reported, the mechanism of hepatotoxicity is unclear.

In conclusion, chronic inflammation is associated with various diseases, and the persistence of inflammation systemically indicates dysfunction and damage of various organs. Plant-derived catechins impart anti-inflammatory and inflammatory response stabilization based on excellent antioxidant activity. This review provides convincing evidence that catechins and plant materials rich in catechins are effective in suppressing inflammatory stress in the short and long term through an inflammatory mechanism in in vivo studies. Therefore, catechins themselves or nutraceutics with catechins can be used as strong anti-inflammatory agents or functional food materials with excellent physiological activity. However, some in vivo and clinical studies have continuously reported that high doses of catechins and green tea extract cause safety concerns and risks of hepatic damage and liver necrosis. Considering these reports, additional studies should be conducted to confirm the empirical evidence of hepatotoxicity pathway, or to make guidelines for stably ingesting catechins by limiting intake so that it does not induce toxicity.

Acknowledgements This research was funded by the Korea Institute of Planning and Evaluation for Technology in Food, Agriculture and Forestry (IPET) through the Export Promotion Technology Development Program, funded by the Ministry of Agriculture, Food and Rural Affairs (MAFRA) (617072-5). This study was supported by the Basic Science Research Program through the National Research Foundation (NRF) of Korea (NRF 2018R1D1A3B07043398) funded by the Ministry of Education, Republic of Korea.

Declarations

Conflict of interest The authors declare that they have no conflict of interest to disclose.

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