The roles of catechins in regulation of systemic inflammation

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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...
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) (Tsuciyia, 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.
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-\(\alpha\) 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-\(\kappa\)B 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 (A\(\beta\)) plaque formation, and damage to the cholinergic system (Ksiežak-Reding et al., 2003; Petry et al., 2020; Zhang et al., 2015). In addition, these dysfunctions in brain...
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 continuously, 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 acetyltransferase (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-kB in immune cells and macrophages, which inhibits the synthesis of pro-inflammatory cytokines and exhibits anti-inflammatory activity (Shenhare-Tsarfary et al., 2014). Thus, inhibition of AChE and butyrylcholinesterase (BChE) by catechins might reduce the inflammatory response by inhibiting the

![Image of Table 1](image)

Table 1 Physiological studies of catechins on Alzheimer’s disease

| Materials  | Dosesa | Species/organ (origin)b | Stressorsc | Biomarkersd | References   |
|------------|--------|-------------------------|------------|-------------|--------------|
| EGCG       | 15 mg/kg (p.o.) | SAMP8 mice/FC, HIP | AD-transgenic | ↑Synaptophysin, PSD95 | Guo et al. (2017) |
|            | 2 μM/well   | BV-2 cells/ Microglia | LPS        | ↑TLR4, nitric oxide, iNOS, TNF-α, IL-1β | Park and Chun (2016) |
|            | 5 mg/kg/day  | SD rats/HP          | Scopolamine | ↑AChE, SOD, LTP, MDA | Kim et al. (2022) |
|            | 50 mg/kg   | APP/PS1 mice/WB     | AD-transgenic | ↑IL-10, IL-13, IL-1β | Bao et al. (2020) |
| Catechin hydrate | 50 mg/kg | Wistar rats/HP, CC | Streptozotocin | ↑GS, GPx, GR, catalase | Ahmed et al. (2013) |
| Green tea catechins | 40 mg/kg of b.w. | BALB/c mice/HP | PM2.5 | ↑SOD, GSH, BCI-2, AChR-3α, ChAT | Kim et al. (2021) |
|            | 50 mg/kg of b.w. | C57BL/6 mice/HC | HFD | ↑p-JNK, p-IκB-α, TNF-α, BAX, Aβ, p-tau, AChE | Kim et al. (2020b) |
| Persimmon catechin | 20 mg/kg of b.w. | ICR mice/ WB | Trime thylamin chloride | ↑SOD, GSH, MPP, ATP, p-Akt | Kim et al. (2018) |

aMaximal dose of referred study. Body weight (b.w.)
bAbbreviation of organs. FC frontal cortex, HIP hippocampus, WB whole brain, CC cerebral cortex
cAbbreviation of stressors. AD Alzheimer’s disease, LPS lipopolysaccharide, PM particulate matter, HFD high-fat diet
dAbbreviation 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, COX-2 cyclooxygenase-2, BCI-2 B-cell lymphoma 2, AChR-3α acetylcholine receptor-3α, ChAT choline acetyltransferase, 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 B-cell lymphoma 2 associated X, BDNF brain derived neurotrophic factor, IDE insulin degrading enzyme, COX-2 cyclooxygenase-2, MPP 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.
Table 2 Physiological studies of catechins on metabolic disease related to high fat diet

| Materials     | Dosesa | Species/organ (origin) | Stressorsb | Biomarkersc | References          |
|---------------|--------|------------------------|------------|-------------|---------------------|
| EGCG          | 50 μM/well | HFD                    | OA         | SOD, catalase, GPx, LC3A/B, Beclin-1, p-ERK | Wu et al. (2021) |
| EGCG          | 50 mg/kg/day | C57BL/6/J          | HFD        | P62, p-JNK, p-p38 | Wu et al. (2021) |
| (Physiological studies of catechins) |        |                        |            | Triglyceride, total cholesterol, ALT, AST, NEFA |                    |

| EGCG          | 0.7 g/day/kg of b.w. (p.o.) | C57BL/6/J adipose tissue | HFD        | HDLC | Raederstorff et al. (2003) |
| Epicatechin   | 200 mg/kg (p.o.) | 3T3-L1 cells/adipocytes | IBMX, DEX  | TNF-α, IL-6, Saa3, Ip-10, Ccl19, cd11c, Cidea | Sano et al. (2017) |
| (+)-Catechin  | 300 μmol/L | Wistar rats (female)/plasma | Semisynthetic diet high in cholesterol and fat | HDLC | Jiang et al. (2019) |
| Green tea catechin | 1.7 mg/day (p.o.) | C57BL/6/J liver | ApoE-deficient transgenic mice | HDLC | 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-1xβ-α, CAE | Relja et al. (2011) |
| Green tea catechin | 50 mg/kg (p.o.) | C57BL/6/J liver | HFD | TNF-α, IL-1β, TNFR1, p-IRS-1, p-JNK, iNOS, COX-2, HMGR, PPARγ, FAS | Kim et al. (2020b) |
| Wine grape seed flour catechin | 5% (w/v) (p.o.) | C57BL/6/J plasma | HFD, HFrD | HDLC | Seo et al. (2020) |

*aMaximal dose of referred study. Body weight (b.w.).

*bAbbreviation of stressors. OA oleic acid, HFD high-fat diet, IBMX isobutylmethylxanthine, DEX dexamethasone, HFrD high-fructose diet

*cAbbreviation 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-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, PPAR peroxisome proliferator activated receptor gamma, SREBP1C sterol regulatory element-binding protein 1C, VLCLD very-low-density lipoprotein cholesterol, MDA malondialdehyde, PMNL polymorphonuclear leukocyte, ICAM-1 intercellular adhesion molecule-1, 1-1xβ-α phosphor-nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, CAE choleoacetate esterase, TNFR/TNF-α receptor 1, p-IRS-1 phosphorylated insulin receptor substrate-1, iNOS inducible nitric oxide synthase, COX-2 cyclooxygenase-2, HMGR 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.
Materials | Doses\(^a\) | Species/organ (origin) | Stressors\(^b\) | Biomarkers\(^c\) | References\\n\hline
EGCG | 6 g/kg/day | Wistar rats/liver | Ethanol | ↑Glycogen, ADH, ALDH, GST ↓AST, ALT, GGT, LDH, cytochrome P450, bilirubin | Anuradha and Kaviaras (2007)\\nEpicatechins | 300 mg/kg (p.o.) | Sprague Dawley rats/liver | CCl\(_4\) | ↓z-SMA, TGF-\(\beta\), p-ERK1/2, p-Smad1, TNF-\(\alpha\), MMP2, MMP9, IL-17 | Wang et al. (2018)\\n(\(+\))-Catechin | 16 g/mL/ well | Huh-7 cells/human hepatoma cells | HCV | ↓COX-2, p-NF-\(\kappa\)B, NS5A-Myc | Lee et al. (2011)\\nGreen tea catechin | 0.1% (w/v) (p.o.) | Sprague Dawley rats/liver | BDL | ↓ALT, procollagen-\(\alpha\)(I), AP-1, z-SMA, 4-HNE, TGF-\(\beta\)1, TNF-\(\alpha\) | Zhong et al. (2003)\\nGreen tea catechin | 50 mg/kg/day (p.o.) | Wistar rats/liver | Sanfenon | ↓AST, ALT, 4-HNE, 8-OHdG, AP-1, TGF-\(\beta\)1, z-SMA | Kobayashi et al. (2010)\\nGreen tea catechin | 10% (w/v) (p.o.) | Hamsters/liver | CCl\(_4\) | ↑GSH, ADH, cytochrome P450 reductase, HDLC | Elgawish et al. (2015)\\nBlack tea catechin | 2% (w/v) (p.o.) | Sprague Dawley rats/liver | Aflatoxin | ↑SOD, catalase, GST, GR, GPx ↓AST, ALT, ALP | Alm-Elddeen et al. (2015)\\n\hline
\(^a\)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, GGTT gamma glutamyl peptide, LDH lactate dehydrogenase, \(\alpha\)-SMA \(\alpha\)-smooth muscle actin, TGF-\(\beta\) transforming growth factor-\(\beta\), p-ERK1/2 phosphorylated extracellular signal-regulated kinase \(\frac{1}{2}\), TNF-\(\alpha\) tumor necrosis factor-\(\alpha\), MMP2 matrix metalloproteinase-2, MMP9 matrix metalloproteinase-9, 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-\(\alpha\)/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-\(\alpha\) and interleukins by upregulating NF-\(\kappa\)B and apoptotic pathways and increasing protein expression of TLR-mediated protein and gene signaling (Doğanıyıgit et al., 2020). In particular, lipid accumulation in hepatic tissue stimulates the activation of immune cells that secrete inflammatory cytokines such as TNF-\(\alpha\) and interleukin 1 beta (IL-1\(\beta\)), 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-\(\kappa\)B 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-1\(\beta\) and TNF-\(\alpha\) 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...
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 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'-

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**Table 4 Physiological studies of catechins on respiratory disease**

| Materials        | Doses<sup>a</sup> | Species/organ (origin) | Stressors<sup>b</sup> | Biomarkers<sup>c</sup> | References |
|------------------|-------------------|------------------------|------------------------|-------------------------|------------|
| EGCG             | 200 mg/kg (p.o.)  | Sprague Dawley rats/lung | Hg, Cd, Cr, Ni, Cu     | Mitochondrial complex I, ATP, SOD, catalase | Wang et al. (2020) |
| Epicatechin      | 500 μM/well       | MRC-5 cells/human lung fibroblast cells | Amiodarone | Mitochondrial complex I, ATP, SOD, catalase | Santos et al. (2017) |
| Catechin Hydrate | 40 mg/kg of b. w. (p.o.) | Swiss albino mice/lung | Benzo(a)pyrene | Mitochondrial complex I, ATP, SOD, catalase | Santos et al. (2017) |
| Catechin         | 100 μg/mL/well    | A549 cells/pulmonary carcinoma | Influenza A (H1N1) virus | Mitochondrial complex I, ATP, SOD, catalase | You et al. (2018) |
| Catechin         | 500 μM/well       | A549 cells/pulmonary carcinoma | Amiodarone | Mitochondrial complex I, ATP, SOD, catalase | Santos et al. (2017) |
| Green tea catechins | 10 μg/mL/well | A549 cells/pulmonary carcinoma | PM<sub>2.5</sub> | Mitochondrial complex I, ATP, SOD, catalase | Santos et al. (2017) |
| Green tea catechins | 40 mg/kg of b.w. (p.o.) | BALB/c mice/lung | PM<sub>2.5</sub> | Mitochondrial complex I, ATP, SOD, catalase | Santos et al. (2017) |

<sup>a</sup>Maximal dose of referred study. Body weight (b.w.)

<sup>b</sup>Abbreviation of stressors. PM particulate matter

<sup>c</sup>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, BCI-2 B-cell lymphoma 2, LPO lipid peroxidation, LDH lactate dehydrogenase, CYPOR crystal structure of a NADPH-cytochrome P450, mEH microsomal epoxide hydrodrolase, 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 BCI-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 BCI-2 associated X, IL-1β interleukin-1β

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**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). Catechins 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.
Table 5  Physiological studies of catechins on gastrointestinal disease

| Materials   | Doses* | Species/organ (origin) | Stressorsb | Biomarkersc | References                    |
|-------------|--------|------------------------|------------|-------------|-------------------------------|
| EGCG        | 100 mg/kg (i.g.) | CF-1 mice/Plasma | Non-stressor | ↑SGLT-1 | Forester et al. (2012)       |
| EGCG        | 1.5 mM (p.o.) | C57BL/6 mice (female/colon, ileum) | DSS | ↑Bowel length, SOD, GPx, ↑MPO, MDA, ↑pSTAT1, nitric oxide, MPO, NF-κB, 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, ↑IFN-γ, ↑TNF-α, ↑calprotectin, ↑IL-6, ↑IL-1β, ↑COX-2, ↑IκBα | Dey et al. (2020) |
| EGCG        | 0.05% (w/w) (p.o.) | ICR mice/colon | DSS | ↑HO-1, p-ERK 1/2, ↑p-IκBα-β, ↑iNOS, ↓COX-2, ↓IL-6, ↓IL-1β, ↓TNF-α, ↓p65, nitric oxide | Chiu et al. (2012) |
| Epicatechin | 300 mg/kg (p.o.) | C57BL/6 J mice/colon | DSS | ↑SOD, GPx, catalase | Zhang et al. (2016) |
| Cocoa       | 500 mg/kg | Balb/C mice (female/colon) | DSS | ↑Bowel length, ↑MPO, IL-6, nitric oxide, COX-2, pSTAT3, pSTAT1α, IL-1β, TNF-α, IFNγ | Andijiar et al. (2011) |
| Green tea   | 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   | 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) |

*Maximal dose of referred study. Body weight (b.w.)

bAbbreviation of Stressors. DSS dextran sulfate sodium, HFD high-fat diet
cAbbreviation of biomarkers. SGLT-1 sodium-glucose transporter-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-IκBα phosphoryl 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

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 (Johansson 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 tussis, 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 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 CCl4-induced fibrotic rat (Wang et al., 2018). Green tea catechins also decreased the expression of procollagen-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.
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 PM2.5-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 probiotics 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 maltophilia* (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 perportal 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 vivo studies. Therefore, catechins themselves or nutraceuticals 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.

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Declarations

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

References

Adler KB and Li Y. Airway epithelium and mucus: intracellular signaling pathways for gene expression and secretion. American Journal of Respiratory Cell and Molecular Biology. 25: 397-400 (2001)
Ahmed ME, Khan MM, Javed H, Vaibhav K, Khan A, Tabassum R, Ashfaq M, Islam F, Safhi MM, Islam, F. Amelioration of cognitive impairment and neurodegeneration by catechin hydrate in rat model of streptozotocin-induced experimental dementia of Alzheimer’s type. Neurochemistry International. 62: 492-501 (2013)
Alipourfard I, Datukishvili N, Mikeladze D. TNF-α downregulation modifies insulin receptor substrate 1 (IRS-1) in metabolic signaling of diabetic insulin-resistant hepatocytes. Mediators of Inflammation. 2019: 3560819 (2019)
Alm-Elddeen AA, Mona MH, Shati AA, El-Mekkawy HI. Synergistic effect of black tea and curcumin in improving the hepatotoxicity induced by aflatoxin B1 in rats. Toxicology and Industrial Health. 31: 1269-1280 (2015)
Andersen OM and Markham KR. Flavonoids: chemistry, biochemistry and applications. CRC press, Boca Raton, FL, USA pp. 472-551 (2005)
Andújar I, Recio MC, Giner RM, Cienfuegos-Jovellanos E, Laghi S, Muguerra B, Rios JL. Inhibition of ulcerative colitis in mice after oral administration of a polyphenol-enriched cocoa extract is mediated by the inhibition of STAT1 and STAT3 phosphorylation in colon cells. Journal of Agricultural and Food Chemistry. 59: 6474-6483 (2011)
Angeloni C, Pirola L, Vauzour D, Maraldi T. Dietary polyphenols and their effects on cell biochemistry and pathophysiology. Oxidative Medicine and Cellular Longevity. 2012: 583901 (2012)
Anuradha CV and Kaviarasan S. (-) Epigallocatechin gallate restores ethanol-induced alterations in hepatic detoxification system and prevents apoptosis. Oriental Pharmacy and Experimental Medicine. 7: 311-320 (2007)
Arts ICW, Hollman PCH, Feskens EJM, de Mesquita HB, Kromhout D. Catechin intake and associated dietary and lifestyle factors in a representative sample of Dutch men and women. European Journal of Clinical Nutrition. 55: 76-81 (2001)
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Bao I, Liu W, Zhou HY, Gui YR, Yang YH, Wu MJ, Xiao Y, Shang J, Long G, Shu XJ. Epigallocatechin-3-gallate alleviates cognitive deficits in APP/PS1 mice. Current Medical Science. 40: 18-27 (2020)

Bazzoni G, Dejana E, Del Maschio A. Platelet-neutrophil interactions. Possible relevance in the pathogenesis of thrombosis and inflammation. Haematologica. 76: 491-499 (1991)

Bedford PA, Todoric V, Westcott ED, Windsor AC, English NR, Al-Hassi HO, Raju KS, Mills S, Knight SC. Adipose tissue of human omentum is a major source of dendritic cells, which lose MHC Class II and stimulatory function in Crohn’s disease. Journal of Leukocyte Biology. 80: 546-554 (2006)

Bertrand D and Wallace TL. A review of the cholinergic system and therapeutic approaches to treat brain disorders. Behavioral Pharmacology of the Cholinergic System. 45: 1-28 (2020)

Botten D, Fugallo G, Fraternali F, Molteni C. Structural properties of green tea catechins. The Journal of Physical Chemistry B. 119: 12860-12867 (2015)

Brückner M, Westphal S, Domschke W, Lüering A. Green tea polyphenol epigallocatechin-3-gallate shows therapeutic antioxidative effects in a murine model of colitis. Journal of Crohn’s and Colitis. 6: 226-235 (2012)

Canbay A, Feldstein AE, Higuchi H, Werneburg N, Grambihler A, Bronk SF, Gores GJ. Kupffer cell engulfment of apoptotic bodies stimulates death ligand and cytokine expression. Hepatology. 38: 1188-1198 (2003)

Cheng X, Shen Y, Li R. Targeting TNF: a therapeutic strategy for Alzheimer’s disease. Drug Discovery Today. 19: 1822-1827 (2014)

Chiou YS, Ma YL, Sang S, Ho CT, Wang YJ, Pan MH. Peracetylated (-)-epigallocatechin-3-gallate (AcEGCG) potently suppresses dextran sulfate sodium-induced colitis and colon tumorigenesis in mice. Journal of Agricultural and Food Chemistry. 60: 3441-3451 (2012)

Church RJ, Gatti DM, Urban TJ, Long N, Yang X, Shi Q, Eaddy S, Mosedale M, Ballard S, Churchill GA, Navarro V, Watkins PB, Threadgill DW, Harrill AH. Sensitivity to hepatotoxicity due to epigallocatechin gallate is affected by genetic background in diversity outbred mice. Food and Chemical Toxicology. 76: 19-26 (2015)

Conti P, Ronconi G, Caraffa, AL, Gallenga CE, Ross R, Frydas I, Kritis SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. Journal of Biological Regulators and Homeostatic Agents. 34: 1 (2020)

Coussens LM and Werb Z. Inflammation and cancer. Nature. 420: 860-867 (2002)

Crespy V and Williamson G. A review of the health effects of green tea catechins in in vivo animal models. The Journal of Nutrition. 134: 3431-3440 (2004).

Czaja AJ. Hepatic inflammation and progressive liver fibrosis in chronic liver disease. World Journal of Gastroenterology. 20: 2515 (2014)

Dey P, Olmstead BD, Sasaki GY, Vodovotz Y, Yu Z, Bruno RS. Epigallocatechin gallate but not catechin prevents nonalcoholic steatohepatitis in mice similar to green tea extract while differentially affecting the gut microbiota. Journal of Nutritional Biochemistry. 84, 108455 (2020)

Dey P, Sasaki GY, Wei P, Li J, Wang L, Zhu J, Zhu J, McGtue D, Yu Z, Bruno RS. Green tea extract prevents obesity in male mice by alleviating gut dysbiosis in association with improved intestinal barrier function that limits endotoxin translocation and adipose inflammation. Journal of Nutritional Biochemistry. 67: 78-89 (2019)

Doganyigit Z, Okan A, Kaymak E, Pandir D, Silici S. Investigation of protective effects of apilarnil against lipopolysaccharide induced liver injury in rats via TLR 4/HMGB-1/NF-kB pathway. Biomedicine & Pharmacotherapy. 125: 109967 (2020)

Elgawish RAR, Rahman HGA, Abdelrazek HM. Green tea extract attenuates CCL4-induced hepatic injury in male hamsters via inhibition of lipid peroxidation and p53-mediated apoptosis. Toxicology Reports. 2: 1149-1156 (2015)

Fan FY, Sang LX, Jiang M. Catechins and their therapeutic benefits to inflammatory bowel disease. Molecules. 22: 484 (2017)

Ferrucci, L. Fabbri E. Inflammaging: chronic inflammation in ageing, cardiovascular disease, and frailty. Nature Reviews Cardiology. 15: 505-522 (2018)

Forester SC, Yu, Lambert JD. Inhibition of starch digestion by the green tea polyphenol, (-)-epigallocatechin-3-gallate. Molecular Nutrition & Food Research. 56: 1647-1654 (2012)

Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology. 134: 1655-1669 (2008)

Friedman SL, Arthur MJ. Activation of cultured rat hepatic lipocytes by Kupffer cell conditioned medium. Direct enhancement of matrix synthesis and stimulation of cell proliferation via induction of platelet-derived growth factor receptors. Journal of Clinical Investigation. 84: 1780-1785 (1989).

Gadkar PV and Balaraman M. Catechins: Sources, extraction and encapsulation: A review. Food and Bioproducts Processing. 93: 122-138 (2015).

Galati G, Lin A, Sultan AM, O’Brien PJ. Cellular and in vivo hepatotoxicity caused by green tea phenolic acids and catechins. Free Radical Biology and Medicine. 40: 570-580 (2006)

Grzesik M, Naparko K, Bartosz G, Sadowska-Bartosz I. Antioxidant properties of catechins: Comparison with other antioxidants. Food Chemistry. 241, 480-492 (2018)

Guo Y, Zhao Y, Nan Y, Wang X, Chen Y, Wang S. (-)-Epigallocatechin-3-gallate ameliorates memory impairment and rescues the abnormal synaptic protein levels in the frontal cortex and hippocampus in a mouse model of Alzheimer’s disease. Neuroreport. 28: 590-597 (2017)

Halaris A. Inflammation, heart disease, and depression. Current Psychiatry Reports. 15: 400 (2013)

Huang F, Pan B, Wu J, Chen E, Chen L. Relationship between exposure to PM2.5 and lung cancer incidence and mortality: a meta-analysis. Oncotarget. 8: 43322 (2017)

Huda-Faujjan N, Abdulamir AS, Fatimah AB, Anas OM, Shuhaimi M, Yazid AM, Loong YY. The impact of the level of the intestinal short chain fatty acids in inflammatory bowel disease patients versus healthy subjects. Open Biochemistry Journal. 4: 53-58 (2010)

Hussain AR, Ahmed SO, Ahmed M, Khan OS, Al AbdulMohsen S, Platanias LC, Al-Kuraya, KS, Uddin S. Cross-talk between NFkB and the PI3-kinase/AKT pathway can be targeted in primary effusion lymphoma (PEL) cell lines for efficient apoptosis. PloS ONE. 7: 39945 (2012)

Iacopini P, Baldi M, Storchi P, Sebastiani L. Catechin, epicatechin, quercetin, rutin and resveratrol in red grape: Content, in vitro antioxidant activity and interactions. Journal of Food Composition and Analysis. 21: 589-598 (2008)

Ingersoll MA, Platt AM, Potteaux S, Randolph GJ. Monocyte trafficking in acute and chronic inflammation. Trends in Immunology. 32: 470-477 (2011)

Isbrucker RA, Edwards JA, Wolz E, Davidovich A, Bausch J. Safety studies on epigallocatechin gallate (EGCG) preparations. Part 2: dermal, acute and short-term toxicity studies. Food and Chemical Toxicology. 44: 636-650 (2006)

Jiang Y, Ding S, Li F, Zhang C, Sun-Waterhouse D, Chen Y, Li D. Effects of (+)-catechin on the differentiation and lipid metabolism of 3T3-L1 adipocytes. Journal of Functional Foods. 62: 103558 (2019)
Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. European Respiratory Journal. 43: 1124-1131 (2014)

Kaihatsu K, Kawakami C, Kato N. Potential anti-influenza virus agents based on coffee ingredients and natural flavonols. Natural Products Chemistry & Research. 2: 2 (2014)

Kajita K, Hojo H, Suzuki M, Nano F, Kumazawa S, Nakayama T. Relationship between antibacterial activity of (+)-catechin derivatives and their interaction with a model membrane. Journal of Agricultural and Food Chemistry. 52: 1514-1519 (2004)

Kaur J. A comprehensive review on metabolic syndrome. Cardiology Research and Practice. 2014: 943162 (2014)

Kelsall BL, Leon F. Involvement of intestinal dendritic cells in oral tolerance, immunity to pathogens, and inflammatory bowel disease. Immunological Reviews. 206: 132-148 (2005)

Keservani RK, Kesharwani RK, Vyas N, Jain S, Raghuvanshi R, Kelsall BL, Leon F. Involvement of intestinal dendritic cells in the pathogenesis of inflammatory bowel disease. Intestinal Research. 13: 11-18 (2015)

Lee JC, Lee YB, Seo WD, Kang ST, Lim JW, Cho KM. Comparative studies of antioxidant activities and nutritional constituents of persimmon juice (Diospyros kaki L. cv. Gapjubaemok). Preventive Nutrition and Food Science. 17: 141-151 (2012)

Lee SB, Lee WS, Shin JS, Jang DS, Lee KT. Xanthotoxin suppresses LPS-induced expression of iNOS, COX-2, TNF-a, and IL-6 via AP-1, NF-kB, and JAK-STAT inactivation in RAW 264.7 macrophages. International Immunopharmacology. 49: 21-29 (2017)

Lee MJ, Maliaikal P, Chen L, Meng X, Bondoc FY, Prabhu S, Lambert G, Mohr S, Yang CS. Pharmacokinetics of tea catechins after ingestion of green tea and (+)-epigallocatechin-3-gallate by humans: formation of different metabolites and individual variability. Cancer Epidemiology and Prevention Biomarkers. 11: 1025-1032 (2002)

Lee JC, Tseng CK, Wu SF, Chang FR, Chiu CC, Wu YC. San-Huang-Xie-Xin-Tang extract suppresses hepatitis C virus replication and virus-induced cyclooxygenase-2 expression. Journal of Viral Hepatitis. 18: 315-324 (2011)

Leon F, Smythies LE, Smith PD, Kelsall BL. Involvement of dendritic cells in the pathogenesis of inflammatory bowel disease. Immune Mechanisms in Inflammatory Bowel Disease. 117-132 (2006)

Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infectious Diseases. 9: 291-300 (2009)

Li S, Strelow A, Fontana EJ, Wesche H. IRAK-4: a novel member of the IRAK family with the properties of an IRAK-kinase. Proceedings of the National Academy of Sciences. 99: 5567-5572 (2002)

Li J, Xu B, Chen Z, Zhou C, Liao L, Qin Y, Yang C, Zhang X, Hu Z, Sun L, Zhu D, Xie P. PI3K/AKT/JNK/p38 signalling pathway-mediated neuronal apoptosis in the prefrontal cortex of mice is involved in the antidepressant-like effect of pioglitazone. Clinical and Experimental Pharmacology and Physiology. 45: 525-535 (2018)

Liu Z, Bruins ME, Ni L, Vincken JP. Green and black tea phenolics: Bioavailability, transformation by colonic microbiota, and modulation of colonic microbiota. Journal of Agricultural and Food Chemistry. 66: 8469-8477 (2018)

Liu J, Lu JF, Wen XY, Kan J, Jin CH. Antioxidant and protective effect of inulin and catechin grafted inulin against CCl4-induced liver injury. International Journal of Biological Macromolecules. 72: 1479-1484 (2015)

Lomax AR and Calder PC. Probiotics, immune function, infection and inflammation: a review of the evidence from studies conducted in humans. Current Pharmaceutical Design. 15: 1428-1518 (2009)

Lontchi-Yimagou E, Sobungi E, Matsha TE, Kengne AP. Diabetes mellitus and inflammation. Current Diabetes Reports. 13: 435-444 (2013)

Martini F, Rosa SG, Klann IP, Fulco BCW, Carvalho FB, Rahmeier FL, Fernandes MC, Nogueira CW. A multifunctional compound
ebselen reverses memory impairment, apoptosis and oxidative stress in a mouse model of sporadic Alzheimer’s disease. Journal of Psychiatric Research. 109: 107-117 (2019)
Mazzanti G, Di Sotto A, Vitolone A. Hepatotoxicity of green tea: an update. Archives of Toxicology. 89: 1175-1191 (2015)
Mishra CB, Pandey P, Sharma RD, Malik MZ, Mongre RK, Lynn AM, Prasad R, Jeon R, Prakash A. Identifying the natural polyphenol catechin as a multi-targeted agent against SARS-CoV-2 for the plausible therapy of COVID-19: an integrated computational approach. Briefings in Bioinformatics. 22: 1346-1360 (2021)
Miura Y, Chiba T, Tomita I, Koizumi H, Miura S, Umezaki K, Hara Y, Ikeda M. Tea catechins prevent the development of atherosclerosis in apoprotein E-deficient mice. Journal of Nutrition. 131: 27-32 (2001)
Musial C, Kuban-Jankowska A, Gorska-Ponikowska M. Beneficial properties of green tea catechins. International Journal of Molecular Sciences. 21: 1744 (2020)
Musso G, Gambino R, Cassader M. Gut microbiota as a regulator of energy homeostasis and ectopic fat deposition: mechanisms and implications for metabolic disorders. Current Opinion in Lipidology. 21: 76-83 (2010)
National Institutes of Health, PubChem. https://pubchem.ncbi.nlm.nih.gov. Accessed Jan 20, 2022.
Onishi S, Mori T, Kanbara H, Habe T, Ota N, Kurebayashi Y, Suzuki T. Green tea catechins adsorbed on the murine pharyngeal mucosa reduce influenza A virus infection. Journal of Functional Foods. 68: 103894 (2020)
Park E and Chun HS. Green tea polyphenol Epigallocatechin gallate (EGCG) prevented LPS-induced BV-2 microglial cell activation. Journal of Life Science. 26: 640-645 (2016)
Park YM, Lim JH, Lee JE, Seo EW. Protective effect of Semisulcospora libertina extract on induced hepatitis in rats. Journal of Life Science. 25: 539-547 (2015)
Patel H, Zaghoul N, Lin KJ, Liu SF, Miller EJ, Ahmed M. Hypoxia-induced activation of specific members of the NF-kB family and its relevance to pulmonary vascular remodeling. International Journal of Biochemistry & Cell Biology. 92: 141-147 (2017)
Petry FDS, Coelho BP, Guelzer MM, Kreutz F, Guma FTCR, Salbego CG, Trindade VMT. Genistein protects against amyloid-beta-induced toxicity in SH-SYSY cells by regulation of Akt and Tau phosphorylation. Phytotherapy Research. 34: 796-807 (2020)
Piai W, Ru LW, Piepenbrink KH, Sundberg EJ, Vogel SN, Toshechakov YY. Recruitment of TLR adapter TRIF to TLR4 signaling complex is mediated by the second helical region of TRIF TIR domain. Proceedings of the National Academy of Sciences. 110: 19036-19041 (2013)
Polosa R, Morjaria JB, Caponnetto P, Prosperini U, Russo C, Pennisi A, Bruno CM. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. Respiratory Research. 17: 1-10 (2016)
Qin XF. Impaired inactivation of digestive proteases by deconjugated bilirubin: the possible mechanism for inflammatory bowel disease. Medical Hypotheses. 59: 159-163 (2002)
Racanelli AC, Kikkers SA, Choi AM, Cloonan SM. Autophagy and inflammation in chronic respiratory disease. Autophagy. 14: 221-232 (2018)
Raederstorff DG, Schlatter MF, Elste V, Weber P. Effect of EGCG on lipid absorption and plasma lipid levels in rats. Journal of Nutritional Biochemistry. 14: 326-332 (2003)
Raetz CR. Biochemistry of endotoxins. Annual Review of Biochemistry. 59: 129-170 (1990)
Rafa H, Amri M, Saoula H, Belkhefia M, Medjebner O, Boutaleb A, Afif S, Nakmouche M, Touil-Boukoffa C. Involvement of interferon-γ in bowel disease pathogenesis by nitric oxide pathway: a study in Algerian patients. Journal of Interferon & Cytokine Research. 30: 691-697 (2010)
Ramnanan CJ, Edgerton DS, Rivera N, Irimia-Dominguez J, Farmer B, Lautz M, Donahue EP, Meyer CM, Roach PJ, Neal DW, Cherrington AD. Molecular characterization of insulin-mediated suppression of hepatic glucose production in vivo. Diabetes. 59: 1302-1311 (2010)
Relja B, Töttel E, Breig L, Henrich D, Schneider H, Marzi I, Lehnert M. Effects of green tea catechins on the pro-inflammatory response after haemorrhage/resuscitation in rats. British Journal of Nutrition. 105: 1791-1797 (2011)
Sano T, Nagayasu S, Suzuki I, Ishiwata M, Yamashita A, Shinjo T, Kushiyama A, Kanematsu T, Nishimura F. Epicatechin down-regulates adipose tissue CCL19 expression and thereby ameliorates diet-induced obesity and insulin resistance. Nutrition, Metabolism and Cardiovascular Diseases. 27: 249-259 (2017)
Santangelo R, Silvestrini A, Mancuso C, Gensinsoides, catechins, quercitin and gut microbiota: Current evidence of challenging interactions. Food and Chemical Toxicology. 123: 42-49 (2019)
Santos LFS, Stolfo A, Calloni C, Salvador M. Catechin and epicatechin reduce mitochondrial dysfunction and oxidative stress induced by amidarone in human lung fibroblasts. Journal of Arrhythmia. 33: 220-225 (2017)
Santos-Buelga C and Scalbert A. Proanthocyanidins and tannin-like compounds–nature, occurrence, dietary intake and effects on nutrition and health. Journal of the Science of Food and Agriculture. 80: 1094-1117 (2000)
Schulze-Osthoff K, Ferrari D, Richemann K, Wesselborg S. Regulation of NF-κB activation by MAP kinase cascades. Immunobiology. 198: 35-49 (1997)
Schwager S and Detmar M. Inflammation and lymphatic function. Frontiers in Immunology. 10: 308 (2019)
Seki E and Schwabe RF. Hepatic inflammation and fibrosis: functional links and key pathways. Hepatology. 61: 1066-1079 (2015)
Sekizawa H, Ikuta K, Mizuta K, Takechi S, Suzutani T. Relationship between polyphenol content and anti-influenza viral effects of berries. Journal of the Science of Food and Agriculture. 93: 2239-2241 (2014)
Selkoe DJ. The molecular pathology of Alzheimer’s disease. Neuron. 6: 487-498 (1991)
Seo KH, Yokoyama W, Kim H. Comparison of polyphenol-rich wine grape seed flour-regulated fecal and blood microRNAs in high-fat, high-fructose diet-induced obese mice. Journal of Functional Foods. 73: 104147 (2020)
Shabbir U, Rubab M, Daliri EBM, Chelliah R, Javed A, Oh DH. Curcumin, quercetin, catechins and metabolic diseases: The role of gut microbiota. Nutrients. 13: 206 (2021)
Shahid A, Ali R, Ali N, Hasan SK, Bernwal P, Afzal SM, Vafa A, Sultana S. Modulatory effects of catechin hydrate against genotoxicity, oxidative stress, inflammation and apoptosis induced by benzo(a)pyrene in mice. Food and Chemical Toxicology. 92: 64-74 (2016)
Shenhar-Tsarfaty S, Berliner S, Bornstein NM, Soreq H. Cholinesterases as biomarkers for parasympathetic dysfunction and inflammation-related disease. Journal of Molecular Neuroscience. 53: 298-305 (2014)
Shlosberg D, Benifla M, Kaufer D, Friedman A. Blood–brain barrier permeability to curcumin, quercetin and gut microbiota: Current evidence of challenging interactions. Food and Chemical Toxicology. 123: 42-49 (2019)
Shon Y, Huang Y, Zhu X, Liu C, Hu Y, Yang H. A review of the possible associations between ambient PM2.5 exposures and the development of Alzheimer’s disease. Ecotoxicology and Environmental Safety. 174: 344-352 (2019)
Sochocka M, Donskow-Lysoniewska K, Diniz BS, Kurpas D, Brozowska E, Leszek J. The gut microbiome alterations and
inflammation-driven pathogenesis of Alzheimer’s disease—a critical review. Molecular Neurobiology. 56: 1841-1851 (2019)
Stalmach A, Mullen W, Steiling H, Williamson G, Lean ME, Crozier A. Absorption, metabolism, and excretion of green tea flavan-3-ols in humans with an ileostomy. Molecular Nutrition & Food Research. 54: 323-334 (2010)
Stojanov S, Berlec A, Strukelj B. The influence of probiotics on the Firmicutes/Bacteroidetes ratio in the treatment of obesity and inflammatory bowel disease. Microorganisms. 8: 1715 (2020)
Takaishi H, Matsuki T, Nakazawa A, Takada T, Kado S, Asahara T, Kamada N, Sakuraba A, Yajima T, Higuchi H, Inoue N, Ogata H, Iwao Y, Nomoto K, Tanaka R, Hibi T. Imbalance in intestinal microflora constitution could be involved in the pathogenesis of inflammatory bowel disease. International Journal of Medical Microbiology. 298: 463-472 (2008)
Taylor PW, Hamilton-Miller JM, Stapleton PD. Antimicrobial properties of green tea catechins. Food Science and Technology Bulletin. 2: 71-81 (2005)
Tian DS, Xie MJ, Yu ZY, Zhang Q, Wang YH, Chen B, Chen C, Wang W. Cell cycle inhibition attenuates microglia induced inflammatory response and alleviates neuronal cell death after spinal cord injury in rats. Brain Research. 1135: 177-185 (2007)
Tsai SY, Gildengers AG, Hsu JL, Chung KH, Chen PH, Huang YJ. Inflammation associated with volume reduction in the gray matter and hippocampus of older patients with bipolar disorder. Journal of Affective Disorders. 244: 60-66 (2019)
Tsuchiya H. Stereospecificity in membrane effects of catechins. Tsai SY, Gildengers AG, Hsu JL, Chung KH, Chen PH, Huang YJ. Inflammation associated with volume reduction in the gray matter and hippocampus of older patients with bipolar disorder. Journal of Affective Disorders. 244: 60-66 (2019)
Tsuchiya H. Stereospecificity in membrane effects of catechins. Chemico-biological Interactions. 134: 41-54 (2001)
Uhal BD, Kim JK, Li X, Molina-Molina M. Angiotensin-TGF-β1 crosstalk in human idiopathic pulmonary fibrosis: autocrine mechanisms in myofibroblasts and macrophages. Current Pharmaceutical Design. 13: 1247-1256 (2007)
Unno K, Pervin M, Nakagawa A, Iguchi K, Hara A, Takagaki A, Nanjo F, Minami A, Nakamura Y. Blood–brain barrier permeability of green tea catechin metabolites and their neurotrophic activity in human neuroblastoma SH-SY5Y cells. Molecular Nutrition & Food Research. 61: 1700294 (2017)
Wang Y, Tang Y, Li Z, Hua Q, Wang L, Song X, Zou B, Ding M, Zhao J, Tang C. Joint toxicity of a multi-heavy metal mixture and chemoprevention in Sprague Dawley rats. International Journal of Environmental Research and Public Health. 17: 1451 (2020)
Wang L, Yang G, Yuan L, Yang Y, Zhao H, Ho CT, Li S. Green tea catechins effectively altered hepatic fibrogenesis in rats by inhibiting ERK and Smad1/2 phosphorylation. Journal of Agricultural and Food Chemistry. 67: 5437-5445 (2018)
Wong J, Magun BE, Wood LJ. Lung inflammation caused by inhaled toxicants: a review. International Journal of Chronic Obstructive Pulmonary Disease. 11: 1391-1401 (2016)
Wu D, Liu Z, Wang Y, Zhang Q, Li J, Zhong P, Xie Z, Ji A, Li Y (2021) Epigallocatechin-3-gallate alleviates high-fat diet-induced nonalcoholic fatty liver disease via inhibition of apoptosis and promotion of autophagy through the ROS/MAPK signaling pathway. Oxidative Med Cell Longevity. 2021:559997
Xu M, Ge C, Qin Y, Gu T, Lv J, Wang S, Ma Y, Lou D, Li Q, Hu L, Wang M, Huang P, Tan J. Activated TNF-α/RIPK3 signaling is involved in prolonged high fat diet-stimulated hepatic inflammation and lipid accumulation: inhibition by dietary fisetin intervention. Food & Function. 10: 1302-1316 (2019)
Xue B, Xie J, Huang J, Chen L, Gao L, Ou S, Wang Y, Peng X. Plant polyphenols alter a pathway of energy metabolism by inhibiting fecal Bacteroidetes and Firmicutes in vitro. Food & Function. 7: 1501-1507 (2016)
Yang CS, Chen G, Wu Q. Recent scientific studies of a traditional Chinese medicine, tea, on prevention of chronic diseases. Journal of Traditional and Complementary Medicine. 4: 17-23 (2014)
Yao HT, Yang YC, Chang CH, Yang HT, Yin MC. Protective effects of (-)-epigallocatechin-3-gallate against acetaminophen-induced liver injury in rats. Biomedicine. 5: 1-6 (2015)
You HL, Huang CC, Chen CJ, Chang CC, Liao PL, Huang ST. Anti-pandemic influenza A (H1N1) virus potential of catechin and gallic acid. Journal of the Chinese Medical Association. 81: 458-468 (2018)
Zand H, Morshedzadeh N, Naghashian F. Signaling pathways linking inflammation to insulin resistance. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 11: 307-309 (2017)
Zhang Y, Darland D, He Y, Yang L, Dong X, Chang Y. Reduction of PM2.5 toxicity on human alveolar epithelial cells A549 by tea polyphenols. Journal of Food Biochemistry. 42: 12496 (2018)
Zhang H, Deng A, Zhang Z, Yu Z, Liu Y, Peng S, Wu L, Qin H, Wang W. The protective effect of epicatechin on experimental ulcerative colitis in mice is mediated by increasing antioxidation and by the inhibition of NF-kB pathway. Pharmacological Reports. 68: 514-520 (2016)
Zhang D, Wang Z, Sheng C, Peng W, Hui S, Gong W, Chen S. Icaritin prevents amyloid beta-induced apoptosis via the PEK/Akt pathway in PC-12 cells. Evidence-Based Complementary and Alternative Medicine. 2015 (2015)
Zhong Z, Groh M, Lehner M, Schoonhoven R, Yang L, Lind H, Lemasters JJ, Thurman RG. Polyphenols from Camellia sinensis attenuate experimental cholestasis-induced liver fibrosis in rats. American Journal of Physiology-Gastrointestinal and Liver Physiology. 285: 1004-1013 (2003)
Zhu YF, Chen JJ, Ji XM, Hu X, Ling TJ, Zhang ZZ, Bao GH, Wan XC. Changes of major tea polyphenols and production of four new B-ring fission metabolites of catechins from post-fermented Jing-Wei Fu brick tea. Food Chemistry. 170: 110-117 (2015)

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