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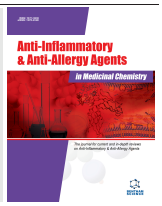

Anti-inflammatory Action of Green Tea

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Abstract: ***Background*:** Green tea has been shown to have beneficial effects against a variety of diseases such as cancer, obesity, diabetes, cardiovascular disease, and neurodegenerative diseases. Through cellular, animal, and human experiments, green tea and its major component, epigallocatechin-3-gallate (EGCG) have been demonstrated to have anti-inflammatory effects. Our previous findings have indicated that green tea and EGCG suppress the gene and/or protein expression of inflammatory cytokines and inflammation-related enzymes.

***Methods*:** Using bibliographic databases, particularly PubMed (provided by the http://www.ncbi.nlm.nih.gov/pubmed, US National Library of Medicine, National Institutes of Health, United States), we examined the potential usefulness of green tea/EGCG for the prevention and treatment of inflammatory diseases in human clinical and epidemiological studies. We also reviewed results from cellular and animal experiments and proposed action mechanisms.

***Results*:** Most of the results from the human studies indicated the beneficial effects of green tea and tea catechins against inflammatory diseases. The cellular and animal studies also provided evidence for the favorable effects of green tea/EGCG. These results are compatible with our previous findings and can be largely explained by a mechanism wherein green tea/EGCG acts as an antioxidant to scavenge reactive oxygen species, leading to attenuation of nuclear factor-κB activity.

***Conclusion*:** Since green tea and EGCG have multiple targets and act in a pleiotropic manner, we may consider their usage to improve the quality of life in patients with inflammatory disease. Green tea and EGCG have beneficial health effects and no severe adverse effects; however, care should be taken to avoid overdosage, which may induce deleterious effects including hepatic injury.

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1. INTRODUCTION

Inflammation is the body's natural immune response to harmful stimuli, such as tissue damage and invading pathogens, and this response is necessary as a defense mechanism to eliminate the hazard [1]. Chronic inflammation causes a variety of diseases including cancer and rheumatoid arthritis (RA) [2, 3]. In the inflammation process, various immune cells such as neutrophils, monocytes, and macrophages, are recruited, which secrete pro- and anti-inflammatory cytokines and enzymes such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, matrix metalloproteinases

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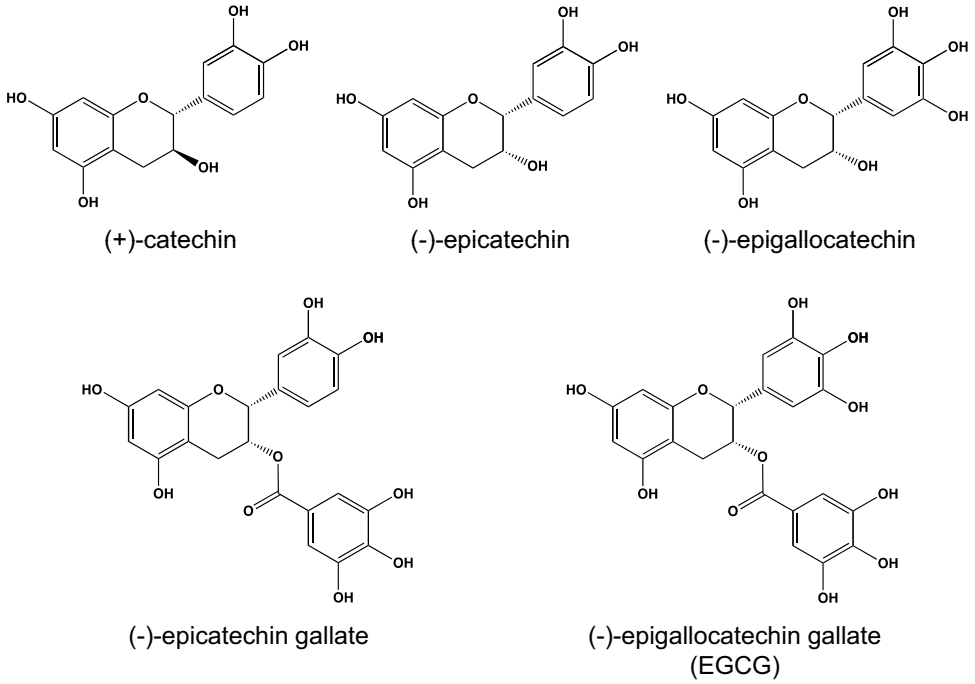

Fig. (1). Chemical structures of (+)-catechin and major green tea catechins.

(MMPs), cyclooxygenases (COXs), and IL-4 [4, 5]. The transcription factor nuclear factor (NF)-κB also regulates genes involved in many inflammatory processes, which play key roles in modulating inflammatory and immune responses [6].

Green tea is one of the most popular drinks in the world and has been studied for its health-promoting properties in various diseases such as cancer, obesity, diabetes, cardiovascular disease, and neurodegenerative diseases [7-10]. Many of the biological effects of green tea are believed to be mediated by its polyphenol catechins (Fig. **1**), and (-)-epigallocatechin-3-gallate (EGCG), which represents 10-15% of total catechins, generally exerts the most effect.

For more than 20 years, we have examined the effect of green tea and green tea catechins (GTCs) on gene/protein expression in cell and animal experiments to reveal their beneficial effects on various diseases [8-10]. The results of such studies showed that green tea and GTCs affected the expression of inflammation-associated genes and proteins such as TNF-α, IL-1β, and MMPs [8-11]. We also demonstrated that EGCG alone and in combination with sulindac, a non-steroidal anti-inflammatory drug (NSAID), reduced precancerous lesions in rat models of azoxymethane (AOM)-induced colon cancer [12] (Table **1**). EGCG and sulindac are known to inhibit COX-1 and COX-2, which are involved in inflammatory regulation [13].

This review summarizes recent findings on the anti-inflammatory properties of green tea and GTCs to reveal their potential usefulness in the prevention and treatment of inflammatory disorders, focusing on the effects of those inflammation-related factors for which we have published our own findings.

2. EFFECT OF GREEN TEA AND GTCS ON TNF-α AND IL-1β

Our animal experiments have shown that a green tea beverage with a high GTC content attenuated the development of galactosamine-induced hepatitis by repressing the gene and protein expression of inflammatory cytokines TNF-α and IL-1β [11] (Fig. **2**). The administration of the beverage also attenuated serum alanine transaminase and aspartate transaminase levels elevated by galactosamine.

Recently, Marinovic *et al*. evaluated the potential of the four main catechins found in green tea (Fig. **1**), in combination and individually, as modulators of human neutrophil functions [14]. Cells derived from the peripheral blood of healthy individuals were cultured with a mixture of 30 μM EGCG, 3 μM (-)-epigallocatechin, 2 μM (-)-epicate-

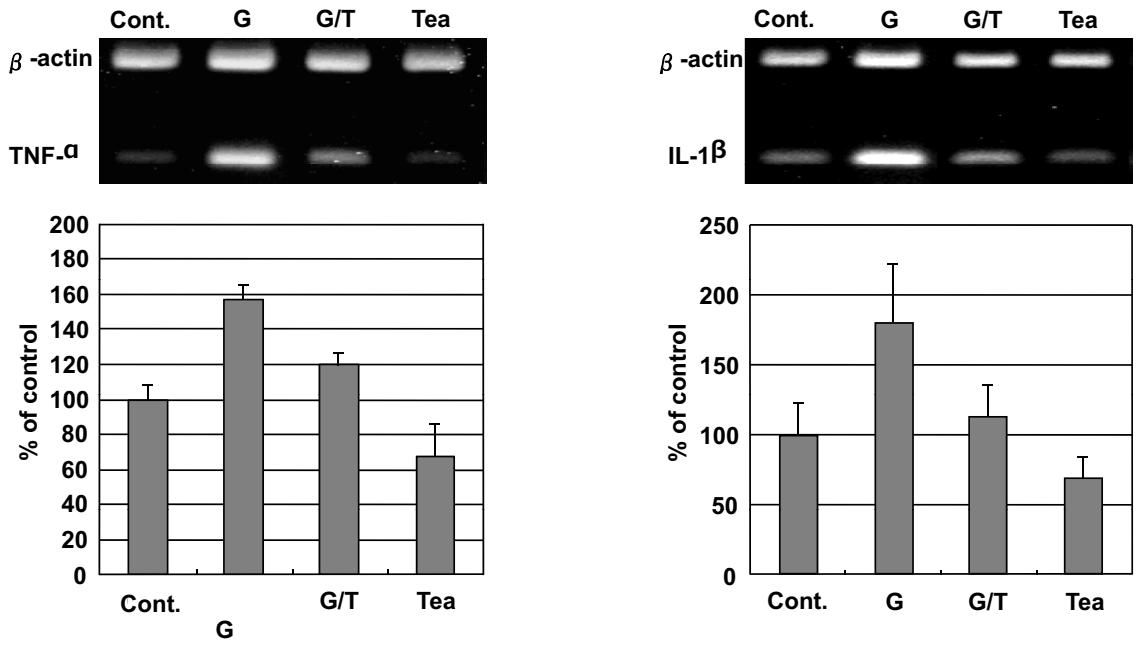

Fig. (2). Gene expression of inflammatory cytokines in galactosamine-induced hepatitis [11]. Galactosamine (G) was injected *i.p.* in rats and the liver samples were examined by quantitative reverse transcription-polymerase chain reaction. G caused the increased levels of hepatic gene expression of TNF-α (left) and IL-1β (right) as compared to that of the saline-treated control group (Cont.). The group given GTC-fortified beverages (G/T) showed attenuated hepatic gene expression of them. The beverage alone had no effects (Tea).

Table 1. Effects of EGCG and sulindac on AOM-induced premalignant lesions in the rat colon [12].

Treatment	Number of ACF/Colon, Mean ± SD
None	0
AOM alone	46.2 ± 4.9
AOM + EGCG	19.5 ± 5.8
AOM + sulindac	21.4 ± 3.4
AOM + EGCG + sulindac	10.0 ± 3.2

F344 male rats treated with AOM with EGCG, sulindac, or both had the significant reduced number of aberrant crypt foci in the colon as compared with the AOM alone group. A combination of EGCG and sulindac resulted in more effective reduction as compared with that by either EGCG or sulindac alone. Cited from [12] with publisher's permission.

chin-3-gallate, and 1.4 μM (-)-epicatechin, or with each individual catechin. It was observed that the catechins, both individually and in combination, reduced the expression of inflammatory factors, such as toll-like receptor-4, nucleic factor-κB (NF-κB), and inducible nitrogen oxide synthase (iNOS), and decreased the release of TNF-α, IL-1β, and IL-6. They also reduced migration capacity and suppressed the production of reactive oxygen species (ROS), nitric oxide, and peroxynitrite, while they increased antioxidant enzyme activities, phagocytic capacity, and calcium release. These results demonstrate that GTCs possess marked inflammation-modulatory activity.

In addition to these results, an increasing amount of evidence has shown that green tea and GTCs have beneficial effects on various inflammation-related diseases through suppression of inflammatory cytokine production as described in the following sections.

3. EFFECT OF GREEN TEA AND GTCS ON TNF-α AND IL-1β IN DISEASES

3.1. Cancer

Proinflammatory cytokines play critical roles in early events during cancer development, and targeting of these cytokines may have potential as a cancer treatment [15]. Fujiki and his coworkers have demonstrated that the anticancer effect of green tea can be correlated to the inhibitory effect on TNF-α gene and protein expression [16]. EGCG has been shown to inhibit NF-κB transcriptional activity in various human cancer cells [17].

NF-κB promotes the production of proinflammatory cytokines [18]. The NF-κB molecule consists of the p50 and p65 subunits, and the activation of NF-κB transcription factor is associated with nuclear translocation of the p65 subunit [19]. This factor is thought to be a potent therapeutic target for cancer prevention and treatment [20, 21]. Chen *et al*. described the potential treatment of ovarian cancer with anti-inflammatory phytochemicals including EGCG [22].

In an experiment to investigate its antimelanoma effects, EGCG inhibited melanoma cell growth at physiological doses (0.1-1 μM) and reduced the activity of NF-κB, while decreasing IL-1β secretion from melanoma cells [23]. The fact that urinary IL-1β levels are elevated in certain patients with cancer indicates that inflammation is associated with cancer progression, suggesting that EGCG's anti-inflammatory activity might be beneficial in treating such patients [24].

Thus, green tea and EGCG might elicit their anticancer effect by repressing the expression and/or activity of NF-κB, TNF-α, and IL-1β. An association of human cancer development with genetic changes caused by carcinogens and proinflammatory cytokines, and simultaneous inflammation induced by proinflammatory cytokines and chemokines has been comprehensively reviewed by Fujiki *et al*. [25].

3.2. Rheumatoid Arthritis (RA) and Osteoarthritis (OA)

RA is an autoimmune disease that attacks the joints and other parts of body. Proinflammatory cytokines such as TNF-α, IL-1β, and IL-17 are involved in the pathogenesis of RA [26, 27]. These cytokines promote chemokine production, recruitment of monocytes into inflammation sites, and osteoclastogenesis, which leads to bone resorption [28, 29]. Therefore, suppression of the production of proinflammatory cytokines is thought to be a promising strategy to treat RA. Because a number of studies have shown that EGCG suppresses expression of proinflammatory cytokines, GTCs could be useful for prevention and progression of RA [30]. A recent review by Riegsecker *et al*. discusses the potential benefits of EGCG in the prevention and treatment of vascular inflammation in RA [3].

In an experiment to investigate the effects of catechin on adjuvant arthritis in the rat, intragastric administration of catechin suppressed secondary inflammatory paw swelling, pain response, and polyarthritis index. Intragastric administration also inhibited production of IL-1β, TNF-α, and prostaglandin E2, and increased cAMP levels in rats with adjuvant arthritis [31].

An experiment using a model of OA demonstrated that mice treated with EGCG exhibited reduced OA-associated pain and that articular cartilage exhibited reduced levels of IL-1β and TNF-α mRNA compared to vehicle controls, demonstrating that EGCG slows OA disease progression and exerts a palliative effect [32].

3.3. Vascular Inflammation

EGCG was shown to inhibit endotoxin-induced expression of TNF-α and IL-1β at both mRNA and protein levels in human cerebral microvascular endothelial cells [33]. Beneficial effects of EGCG in prevention and treatment of vascular inflammation have been discussed by Riegsecker *et al*. [3].

3.4. Liver Injury

As mentioned above, our animal experiments showed that green tea with a high GTC content restored the gene and protein levels of proinflammatory cytokines in galactosamine-induced hepatitis [11]. Similar observations have been reported in concanavalin A- and carbon tetrachloride-induced liver injury in rodents [34-36].

The results of a study to determine the effect of EGCG on concanavalin A-induced hepatitis showed that mice pretreated with EGCG exhibited lower increase in alanine transaminase and aspartate transaminase levels in plasma, reduced inflammatory infiltration, and hepatocyte apoptosis in liver compared with vehicle-treated control mice. EGCG-pretreated mice had abrogated NF-κB and interferon (IFN)-γ at both protein levels in plasma and mRNA levels in liver [35].

When mice were administered with carbon tetrachloride, the mRNA expression levels of TNF-α, COX-2, iNOS, α-smooth muscle actin, transforming growth factor (TGF)-β1, procollagen-I, MMP-2, MMP-9 and tissue inhibitors of MMP (TIMPs) were increased, together with an increase in the activity of NF-κB. Treatment with EGCG signifi-

cantly reduced liver injury, oxidative stress, and the inflammatory response. EGCG also reduced the expression of all of the assayed profibrogenic markers except TIMP-2 and MMP-9. Thus, the protective effect of EGCG may in part be a consequence of the reduction in oxidative stress and the proinflammatory response [36].

Bharrhan *et al*. found that catechin suppressed an array of signaling molecules and modulated alcohol-induced endotoxin-mediated liver injury in a rat model [37]. Xiao *et al*. found that EGCG attenuated fibrosis, oxidative stress, and inflammation in a non-alcoholic fatty liver disease rat model through the TGF/phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt), and NF-κB pathway [38].

In a study of methionine- and choline-deficient diet-induced nonalcoholic steatohepatitis, it was found that EGCG significantly prevented liver damage and body weight loss, and reduced the elevation of plasma transaminase levels. EGCG treatment inhibited IL-1β, IL-6, TNF-α, and monocyte chemotactic protein-1 mRNA expression [39].

In bile duct-ligated rats, EGCG treatment ameliorated liver necrosis, inflammation, and fibrosis, and suppressed expression of the genes associated with liver inflammation and fibrogenesis, such as TNF-α, IL-1β, TGF-β1, MMP-9, and a type I collagen subunit chain [40]. The EGCG's effect may be due to modulation of mitochondrial oxidative stress and inflammation [41].

In an experiment using lipopolysaccharide (LPS)-stimulated L02 hepatocytes, EGCG reduced the production of inflammation-related factors including TNF-α, nitric oxide, and MMP-2. The effect of EGCG was related to the inhibition of NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways. The result demonstrates EGCG's hepatocyte-protective activity [42].

3.5. Ischemia

In a hepatic ischemia-reperfusion experiment, rats were fed a powdered diet containing 0-0.3% green tea extract (GTE) for 5 days [43]. Dietary GTE (0.1%) reduced transaminase release by over 85% and almost totally blocked pathological changes. Hepatic ischemia-reperfusion activated NF-κB and increased TNF-α mRNA and protein expression. These effects were blocked by GTE. Similarly, Giakoustidis *et al*. reported that in a rat hepatic ischemia/reperfusion model experiment, administration of EGCG protected liver by down-regulating the NF-κB and c-Jun signal transduction pathways [44].

In rat models of intestinal ischemia reperfusion, Zhang *et al*. found that the administration of EGCG significantly alleviated the pathological changes in the injured intestine and suppressed the upregulated mRNA and protein expression of TNF-α, IL-1, and IL-6 in the serum and intestine [45].

In an experiment to evaluate the effect of EGCG on apoptosis and damage in testicular seminiferous tubules derived from rats with ischemia/reperfusion-induced inflammation, testicular concentration of TNF-α, IL-1β, and IL-6 was elevated by ischemia. Rats injected with EGCG after ischemia induction showed reduced levels of the three cytokines, similar to the sham level [46].

3.6. Brain Disorders

LPS-mediated systemic inflammation plays a critical role in neurodegenerative diseases. When macrophages were treated with LPS, expression of proinflammatory cytokines (TNF-α, IL-1β, and IL-6) was induced, whereas EGCG pretreatment of macrophages inhibited LPS-mediated induction of these cytokines. EGCG treatment of neurons inhibited LPS-induced production of ROS, suggesting that EGCG represents a potent and useful neuroprotective agent for inflammation-mediated neurological disorders [47].

In a study to examine the neuroprotective effects of EGCG after transient middle cerebral artery occlusion, rats were treated intraperitoneally with EGCG (50 mg/kg) or vehicle immediately after reperfusion. EGCG prevented the impairment of neurological function and decreased the infarct volume, compared with the vehicle group. The upregulation of TNF-α, IL-1β, and IL-6 levels caused by ischemia/reperfusion was significantly ameliorated by EGCG. EGCG also inhibited the upregulation of NF-κB, and induction of COX-2 and iNOS. Thus, EGCG may be a promising therapeutic agent for cerebral ischemia/reperfusion injury, through attenuation of inflammation [48].

Infrasound, a common type of environmental noise and major contributor to vibroacoustic disease, can induce central nervous system damage. Cai *et al*. showed that, after 1-, 2-, or 5-day exposure of rats to 16 Hz, 130 dB infrasound (2 h/day), EGCG significantly inhibited infrasound-induced microglial activation in the rat hippocampal region, as evidenced by reduced expression of a marker for microglia and proinflammatory cytokines (IL-1β, IL-6, IL-18, and TNF-α), as well as suppression of neuronal apoptosis in rat hippocampi. EGCG ameliorated infrasound-induced decreases in inhibitor of κB (IκB) in microglia and attenuated infrasound-induced increases in nuclear NF-κB p65 and phosphorylated IκB-α. These findings suggest that EGCG can be used as a promising drug for the treatment of infrasound-induced central nervous system damage [49].

Syed Hussein *et al*. demonstrated that (+)-catechin exhibited anti-inflammatory effects in LPS-stimulated BV-2 cells by suppressing the production of proinflammatory mediators (TNF-α and IL-6) and the mitigation of NF-κB through Akt/extracellular signal-regulated kinase (ERK)/p38 MAPK, and AMP-activated protein kinase (AMPK) pathways [50]. These findings are very similar to those obtained using EGCG, as described above.

In an autoimmune encephalomyelitis model, EGCG reduced clinical severity by limiting brain inflammation and neuronal damage, and involvement of EGCG's control of NF-κB *via* its antioxidative effect was proposed [51].

3.7. Periodontitis

Porphyromonas gingivalis causes inflammation and leads to periodontitis in gingival tissue damage and bone resorption. To determine whether continuous oral intake of EGCG would alleviate *P. gingivalis*-induced periodontitis, mice were challenged with *P. gingivalis*. The challenged group showed markedly increased alveolar bone resorption of the maxillae, and administration of EGCG resulted in a significant reduction in bone loss. Highly positive areas of IL-17 and IL-1β in the gingival tissue were observed in the challenged groups, and were reduced by EGCG treatment. The elevated expressions of IL-1β, IL-6, IL-17, IL-23, TNF-α, and other mediators in gingival tissue after *P. gingivalis*-challenge were reduced by EGCG treatment, with the exception of IL-23. These results suggest that the anti-inflammatory effect of EGCG is useful in alleviating *P. gingivalis*-induced periodontitis [52].

3.8. Other Diseases

Cao *et al*. reported that EGCG prevented inflammation by reducing macrophage infiltration and inhibiting TNF-α signaling in the pancreas of rats on a high-fat diet. The result suggests that EGCG may be beneficial in diabetes for increasing insulin sensitivity [53].

The tissue accumulation of uric acid leads to the formation of crystalline deposits, which triggers endothelial dysfunction and the onset of an inflammatory response. Human umbilical vein endothelial cells were subjected to uric acid with or without EGCG treatment. Uric acid increased the expression of IL-6, intercellular adhesion molecule-1, TNF-*α*, and monocyte chemotactic protein-1, and the production of ROS in these cells. EGCG suppressed the expression of inflammatory cytokines and ROS generation, suggesting it could be an effective approach to decrease inflammation and oxidative stress induced by uric acid, which is overproduced in gout [54].

In an experiment in which inflammation was induced in differentiated 3T3-L1 adipocytes by LPS, EGCG inhibited inflammation by reducing inflammatory mediator and cytokine levels, including phosphorylated NF-κB, TNF-α, and IL-6. The 67 kDa laminin receptor, toll-like receptor-4 signaling, and glucose transporter-4 were all involved in EGCG's mechanism of action [55].

In an experiment using a non-obese type-2 diabetes animal model, Goto-Kakizaki rats were fed a control high-fat diet or a high-fat diet containing 0.1%, 0.2%, or 0.5% EGCG for 25 weeks. Oxidative stress markers were reduced on supplementation with EGCG at 0.1%, but not at 0.2% or more. Significant reductions in the mRNA levels of genes related to inflammatory responses such as TNF-α, IFN-γ, IL-1β, IL-6, and IL-18 were observed in peripheral leukocytes with EGCG supplementation at 0.1%, but not at 0.2% or more, compared with the control diet without added EGCG. The results suggest that supplementation with a low dose of EGCG reduces oxidative stress and the expression of genes involved in inflamma-

tion in rat peripheral leukocytes [56]. Similar inflammatory responses were also found in the mesenteric adipose tissue of these rats [57].

In an experiment in which rats were fed a high-fat diet, administration of EGCG decreased the fasting plasma level of free fatty acids and insulin. The levels of toll-like receptor-4, Iκ-B kinase β, phosphorylated NF-κB, TNF-α, and IL-6 in the adipose tissues from the EGCG group were all significantly lower than those from the high fat diet control group. EGCG may improve insulin signaling by modulating diet-induced inflammation in adipose tissues [58].

Inflammation plays a role in the pathogenesis of hypertension. A time-dependent increase in mRNA expression of both IL-6 and MMP-9 was observed in human leukaemic monocytic cell line THP-1 macrophages when cultured in normocholesterolemic hypertensive sera. GTC treatment prevented the increase in expression of IL-6 and MMP-9. The results suggest the presence of some humoral factors in hypertensive sera, which may be responsible for changing the phenotype of THP-1 macrophages to express genes with atherosclerotic potential, and that EGCG can modulate their expression [59].

Turner reviewed recent findings of the effect of EGCG on immune-mediated glomerulonephritis, and proposed mechanisms in which EGCG attenuates kidney injury by acting as an antioxidant leading to inhibition of ROS generation and downregulation of renal expression of anti-inflammatory factors including NF-κB, nitric oxide, and iNOS. The author expects future studies to investigate whether this result can be translated to the treatment of patients with glomerulonephritis in clinical practice [60].

4. EFFECT OF GREEN TEA AND GTCS ON CYCLOOXIGENASES IN DISEASES

4.1. Cancer

There is accumulating evidence that inflammation plays important roles in the occurrence and development of cancer [61, 62]. While acute inflammation suppresses cancer, for example, acute inflammation induced by *Mycobacterium bovis bacillus Calmette-Guérin* suppresses bladder cancer cell growth and has been utilized for 30 years as an effective bladder cancer treatment [63], chronic inflammation promotes cancer development [2]. Therefore, drugs and natural products that have anti-inflammatory effects appear to be useful for cancer prevention and therapy. Targeting inflammation-inducing immune cells, which retain more stable genomes than cancer cells, may produce a better outcome, since genomic instability leads to genetic heterogeneity of tumors, which contributes to the development of resistance to therapy [64].

Epidemiological studies have suggested that NSAIDs such as aspirin and sulindac have chemopreventive effects on colon, lung, esophagus, and stomach cancers [65, 66]. Animal model studies have also demonstrated that NSAIDs suppress the development of chemical carcinogen-induced colon cancers [67, 68]. NSAIDs inhibit COX-1 and COX-2 enzymes, which convert arachidonic acid into prostaglandins, leading to induction of inflammatory reactions [69]. While COX-1 is a housekeeping enzyme, is constitutively expressed and controls homeostasis in many tissues, COX-2 is an inducible isoform readily upregulated by inflammatory stimuli [70]. Rigas *et al.* reported that COX-2 overexpression occurred during colon tumorigenesis, and COX-2 inhibition by NSAIDs was chemopreventive for colon cancer [71].

EGCG may inhibit COX-2 without affecting COX-1 expression in human prostate cancer cells [72]. EGCG inhibits melanoma cell migration through suppression of endogenous COX-2 expression and the subsequent release of prostaglandin E2; inactivation of the COX-2 upstream regulator NF-κB was associated with this mechanism [73]. Hwang *et al*. reported that EGCG strongly activates AMPK, which is thought to exert anti-inflammatory actions, and inhibits COX-2 expression, suggesting that AMPK has a role in regulating COX-2 expression [74]. Also, GTE and EGCG downregulated COX-2 expression induced by phorbol ester in mouse skin and in human mammary cells [75].

Intriguingly, Suganuma *et al*. reported that the combination of EGCG and NSAIDs showed synergistic anticancer effects in human lung cancer cells and in mice [16]. In agreement with this finding, we found that EGCG reduced the numbers of aberrant crypt foci, a type of preneoplastic lesion, in rat colon and anticancer efficacy was enhanced with sulindac in an AOM-induced model of colon

carcinogenesis [12] (Table **1**). Although the precise mechanism of action of a combination of EGCG and NSAIDs is not fully understood, this effect might result, at least in part, from COX-2 inhibition. In an experiment using an inflammation-related carcinogenesis model, mice that received intraperitoneal injection of AOM followed by dextran sodium sulfate treatment, EGCG and GTCs showed suppressed multiplicity and volume of colonic neoplasms compared to those untreated with EGCG or GTCs. Treatment with EGCG or GTCs decreased the protein and mRNA expression levels of COX-2 and the mRNA expression of inflammatory cytokines (TNF-α, IFN-γ, IL-6, IL-12, and IL-18) in the colonic mucosa. The results suggest that the inhibitory effects of GTCs on inflammation are related to the suppression of cancer development [76].

4.2. Other Diseases

Chronic hepatitis C viral infection is the leading risk factor for hepatocellular carcinoma and chronic liver disease worldwide. Lin *et al*. illustrated that (+)-epicatechin and (-)-epicatechin inhibited virus replication. In addition to suppressing virus-induced COX-2 expression, they produced prominent anti-inflammatory effects by inhibiting the gene expression of TNF-α, IL-1β, and iNOS, as well as COX-2 in viral protein-expressing hepatoma Huh-7 cells. The results suggest that (+)-epicatechin and (-)-epicatechin may serve as therapeutic supplements for treating hepatitis C virus-related diseases [77].

Wu *et al*. demonstrated that naturally occurring flavonoids including catechin and EGCG attenuated high glucose (15 mM)-induced inflammation in human monocytes. These flavonoids inhibited high glucose-induced expression of proinflammatory genes and proteins, including TNF-α, IL-1β, and COX-2, at a concentration of 20 μM [78]. They also prevented oxidative stress in activated monocytes and inhibited NF-κB by a mechanism which included downregulation of the mRNA expression of receptor of advanced glycation end-products. These flavonoids may prevent hyperglycemia-associated inflammation and atherosclerosis.

In calvarial organ cultures, LPS-induced bone resorption was suppressed by EGCG. In osteoblasts, EGCG suppressed the LPS-induced expression of COX-2 mRNA as well as prostaglandin E2 production. EGCG attenuated LPS-induced bone resorption of mandibular alveolar bones and inhibited the loss of mouse alveolar bone mass *in vivo*, suggesting the beneficial function of EGCG in inflammatory bone resorption [79].

In an experiment on rat spinal cord injury, samples were taken 24 hours after trauma. EGCG-treatment attenuated myelin degradation and TNF-α, IL-1β, nitrotyrosine, iNOS, COX-2, and poly (ADP-ribose) polymerase expression, suggesting that EGCG may be effective in protecting the tissue from secondary damage by modulating inflammatory reactions [80].

Cigarette smoking is a major risk factor for cardiovascular diseases. In an animal model experiment, rats were exposed to side stream cigarette smoke for a period of 12 weeks and were simultaneously administered EGCG orally (20 mg/kg/day). The cigarette smoke exposure increased cardiac injury markers and lipidemic anomalies in serum and myocardium. Supplementation with EGCG reversed these abnormalities and reduced elevated levels of NF-κB, COX-2, TNF-α, and iNOS in heart. Thus, the antioxidant EGCG may exert a cardio-protective effect through prevention of cardiac inflammation *via* reduction of oxidative stress [81].

5. EFFECT OF GREEN TEA AND GTCS ON MATRIX METALLOPROTEINASES IN DISEASES

5.1. Cancer

It is well known that MMPs are deeply involved in inflammation as exemplified by the study in which MMP-9 was shown to modulate inflammation and contribute to the severity of dextran sodium sulfate-induced colitis [82]. Endogenous MMP-9 has also been shown to promote rheumatoid synovial fibroblast survival, inflammation, and cartilage degradation [83].

In a tumor microenvironment, the inflammatory cells such as neutrophils, macrophages, and mast cells produce MMPs including MMP-2 and MMP-9 [84]. Additionally, MMPs are expressed in a wide variety of human cancers, and they can influence the cancer environment by promoting angiogenesis, cell invasion, and metastasis [85]. Hence, MMP expression is associated with cancer aggres-

siveness and patient prognosis [86]. A comprehensive review by Egeblad and Werb summarized the roles of MMPs in cell growth, survival, angiogenesis, invasion, inflammation, and immune surveillance in cancer [87].

During cancer invasion and metastasis, MMPs are required for degradation of the basement membrane and stromal matrix as cancer cells invade adjacent tissue. We demonstrated that EGCG inhibited enzyme activities and gene expression of MMPs, including MMP-2, MMP-3, and MMP-9 [88-90]. In agreement with our study, green tea catechins (0.1% in drinking water) inhibit MMP-2 and MMP-9 in transgenic adenocarcinoma of the mouse prostate mice [91]. Moreover, EGCG inhibits MMP-2 and MMP-9 activity in the human endothelial cells [92]. Later studies have reported similar activities of GTCs on MMPs [93, 94]. However, it is not fully understood how GTC inhibition of the proinflammatory activity of MMPs can be related to their anticancer activity.

5.2. Other Diseases

In an experiment using animals with tendinitis, green tea treatment regulated the activity of MMPs 2, 8, and 9, and induced the synthesis of type I collagen, glycosaminoglycans, and non-collagenous proteins. Green tea may modify extracellular matrix components to facilitate recovery and repair [95].

In an asthma mouse model, mucus production, mucin-5B expression, p38 MAPK, and MMP-9 expression in the asthma group were significantly higher than in the control group. EGCG supplementation resulted in lower levels of these markers in the asthma group [96]. In nasal epithelial cells of patients with allergic rhinitis, EGCG significantly decreased phorbol ester-induced mucin-5B and MMP-9 expression. The results suggest that EGCG may be beneficial in the treatment of allergic airway inflammation [96].

In toluene diisocyanate-induced asthmatic model mice, matrix MMP-9 expression in lung tissues as well as TNF-α and IL-5 production in bronchoalveolar lavage fluid were elevated compared with untreated control mice. Administration of EGCG resulted in reduced asthmatic reaction and diminished ROS generation in the lavage fluid, suggesting that EGCG may be useful as an adjuvant therapy for bronchial asthma [97].

6. CLINICAL TRIALS

A number of epidemiological and intervention studies have revealed beneficial effects of green tea and GTE on various diseases including cancer, diabetes, metabolic syndrome, liver diseases including gastritis, and neurodegenerative diseases [7, 9]. However, only a limited number of results in these studies has provided evidence to indicate that anti-inflammatory activity contributes to the effects.

One example is a double-blind, placebo-controlled trial, in which 56 obese, hypertensive subjects were randomized to receive a daily supplement of 1 capsule containing either 379 mg of GTE or a placebo. After 3 months of supplementation, considerable reductions in fasting serum glucose, insulin levels, and insulin resistance were observed in the GTE group compared with the placebo group. Serum TNF-α and C-reactive protein were significantly lower and total antioxidant status increased in the GTE group compared with the placebo group [98].

On the other hand, several other studies have failed to show positive effects of green tea and GTCs on inflammation-related disorders. For example, in a clinical trial in which 59 smoking healthy volunteers participated, 4-week administration of black tea, green tea, GTE, and water had no effect on inflammation, hemostasis, and endothelial markers, whereas there was a significant negative correlation between the levels of the antioxidant β-carotene and the inflammation markers IL-6 and fibrinogen [99]. Furthermore, recent meta-analysis of data from randomized controlled trials did not indicate a significant effect of supplementation with GTCs on plasma C-reactive protein concentrations [100]. In a double-blind, randomized, placebo-controlled trial to examine the effect of GTCs on UV radiation-induced inflammation, healthy adults (18-65 years old) were randomly allocated to receive 1350 mg encapsulated green tea extract (540 mg GTCs) with 50 mg vitamin C, or placebo, twice daily for 3 months. Volunteers were assigned to the active (n = 25) or the placebo (n = 25) group. The results showed that oral GTC supplementation did not significantly reduce skin erythema, leukocyte infiltration, or eicosanoid response to this inflammatory challenge [101]. Nevertheless, it seems that recently a growing number of reports on clinical trials have

produced promising data on the beneficial effects of green tea and GTCs through anti-inflammatory activity as described below.

Acne vulgaris is a highly prevalent skin disorder characterized by hyperseborrhea, inflammation, and *Propionibacterium acnes* overgrowth. EGCG significantly improved acne in an 8-week randomized, split-face clinical trial, and was well tolerated. The results provide a therapeutic rationale for the use of EGCG in acne [102].

Thirty patients participating in a study were divided randomly into two groups; each group of 15 patients was prescribed either chlorhexidine or green tea mouthwash. There was a significant decrease in plaque index, gingival index, and bleeding index in both groups. However, green tea mouthwash resulted in a statistically significant decrease in bleeding index compared to the chlorhexidine group. There was no significant difference in tooth and tongue staining between the groups. The green tea-containing mouthwash was equally effective on reducing gingival inflammation and plaque as chlorhexidine [103].

In another study, 48 subjects who had teeth with probing pocket depth of 5-10 mm were randomly allocated into the test or control group [104]. Subjects received repeated subgingival application of green tea gel or placebo gel. The results indicated that green tea gel provided more benefit in reducing bleeding on probing and gingival inflammation, when used as an adjunct to non-surgical periodontal treatment. Similarly, Chava and Vedula reported that adjunctive local drug therapy with thermo-reversible green tea gel reduced pockets and inflammation during the 4 weeks of the clinical trial in patients with chronic periodontitis [105].

A randomized controlled clinical trial conducted on 110 male subjects (18-60 years old) found that those who performed a rinse twice daily for 1 min with 10 mL of mouthwash containing 2% green tea had lower mean plaque index and gingival index scores compared with the control placebo group [106]. The results showed that the green tea mouthwash was effective in the reduction of plaque formation and gingivitis.

A pilot intervention study found that GTE had a positive effect for safely managing allergic contact dermatitis, although its potency and efficacy were not strong enough to control allergy skin lesion of moderate severity [107]. Also, in a clinical study to investigate the therapeutic efficacy and safety of GTE for treatment of atopic dermatitis, 4 patients with atopic dermatitis associated with *Malassezia sympodialis* underwent GTE treatment 3 times per week for 4 weeks. All patients showed marked improvement on the mean scoring atopic dermatitis and visual analogue scale, and a significant decrease in the mean values of serum eosinophil counts after treatment. Bath therapy with green tea extract is an effective, safe, and nonsteroidal therapy for treatment of patients with atopic dermatitis associated with *M. sympodialis* [108].

Periostat (doxycycline hyclate) is the only MMP inhibitor that has been approved by the U.S. Food and Drug Administration for the treatment of periodontal disease. Now, several clinical trials using Periostat in combination with standard chemotherapeutics are recruiting patients with polycystic ovarian cancer [109]. Therefore, MMP-inhibiting GTCs may be proposed as a similar drug.

These results are encouraging, however, we need further evidence based on intervention studies, such as that reported by Dominiak *et al*. [110]. In their study, human volunteers were administered 2 capsules containing a mixture of natural antioxidants including EGCG for a period of 2 weeks, and blood samples were collected pre- and post-intervention. Purified lymphocytes were subjected to *ex vivo* exposure to TNF-α or used as untreated controls. The results indicated that the mean NF-κB DNA binding activity was increased upon TNF-α treatment in pre-intervention samples, whereas TNF-α was unable to induce NF-κB in post-intervention samples, suggesting that the mixture could be useful to protect humans against oxidative stress [110]. This example should guide future studies using various test agents for the prevention and treatment of human malignancies in which an anti-inflammation mechanism is involved.

7. ACTION MECHANISM OF EGCG

As has been demonstrated by many researchers, green tea and GTCs can exert anti-inflammatory actions as an antioxidant, and the central target of these agents is thought to be ROS. Green tea and GTCs are able to scavenge ROS, which activate NF-κB to upregulate expression of inflammatory

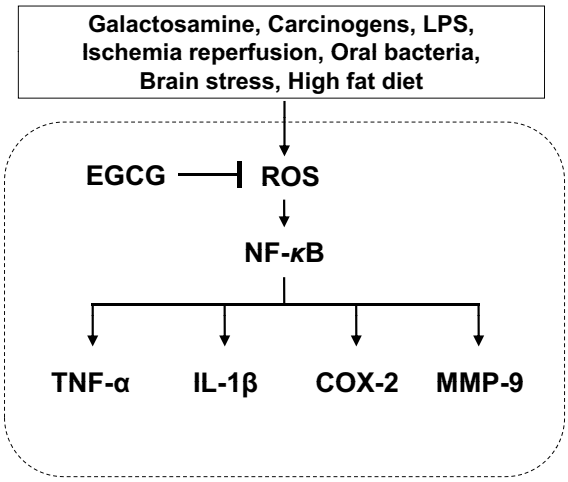

Fig. (3). Anti-inflammation action of EGCG. ROS generated by various extracellular inflammatory stimuli activate NF-κB, a transcriptional factor that upregulates gene expression of proinflammation-related proteins including TNF-α, IL-1β, COX-2, and MMP-9 [10, 18, 73, 111, 112]. EGCG acts as an antioxidant to scavenge ROS, leading to attenuation of the effects of ROS.

cytokines and inflammation-related enzymes including TNF-α, IL-1β, COX-2, and MMP-9 [10, 18, 73, 111, 112] (Fig. **3**). Therefore, suppression of NF-κB activation by green tea and GTCs as an antioxidant would result in their anti-inflammatory effects. It may be expected that various antioxidants, such as plant polyphenols, could have the similar anti-inflammatory effects through an action mechanism similar to that of green tea and GTCs.

It is also possible that different signaling pathways may be involved in the anti-inflammatory action of green tea and GTCs. As described above, (+)-catechin exhibited anti-inflammatory effects through modulation of the Akt/ERK/p38-MAPK pathway and AMPK pathway [50]. The pathway involving 67 kDa laminin receptor may also be an EGCG's target [55, 113]. Singh *et al.* have proposed that, in addition to anti-ROS activity, EGCG can inhibit the inflammatory responses in RA through blocking multiple steps in the Janus kinase/signal transducers and activators of transcription pathway and the MAPK/ERK/AP-1 pathway [114]. Yoon *et al.* demonstrated that EGCG suppressed inflammation and dermal matrix degradation through inhibition of the insulin receptor substrate-1/PI3K/Akt pathway and activation of AMPK, both of which are deeply associated with acne development [102]. In these cases, an EGCG's protein-binding nature [7, 8] appears to be involved. Future studies are required to know whether or not the actions of green tea and/or GTCs can be explained by a unified mechanism.

CONCLUSION

In this review, we illustrated the preventive and therapeutic effects of green tea and GTCs in inflammatory diseases, and discussed these effects with reference to our own findings. Antioxidative activity can explain most of the results presented here, although prooxidative activity of green tea and GTCs might be involved in their suppressive effects on certain diseases including cancer [7, 10, 115].

To improve the quality of life of patients with inflammatory disease, we may consider the usage of green tea and EGCG, because they have multiple targets and act in a pleiotropic manner. Green tea and EGCG have been shown to exert beneficial health effects without severe adverse effects, although care should be taken to avoid the overdosage of supplements, which may induce deleterious effects including hepatic injury [9, 116]. The recent epidemiological discovery that green tea intake decreases the risk of cognitive dysfunction [117, 118] and preclinical results on brain functions as discussed above, suggest that tea drinking may be recommended to help enjoy a high quality of life and long-term health.

LIST OF ABBREVIATIONS

Akt	=	Protein kinase B
AMPK	=	AMP-activated protein kinase
AOM	=	Azoxymethane
AP-1	=	Activation protein 1
COX	=	Cyclooxygenase
EGCG	=	(-)-epigallocatechin gallate
GTC	=	Green tea catechin
GTE	=	Green tea extract
IFN	=	Interferon
IL	=	Interleukin
iNOS	=	Inducible nitrogen oxide synthase
IκB	=	Inhibitor of κB

LPS = Lipopolysaccharide

MAPK = Mitogen activated kinase

MMP = Matrix metalloproteinase

NF-κB = Nucleic factor-kappaB

NSAID = Nonsteroidal anti-inflammatory drug

OA = Osteoarthritis

PI3K = Phosphatidylinositol-3-kinase

RA = Rheumatoid arthritis

ROS = Reactive oxygen species

TGF = Transforming growth factor

TIMP = Tissue inhibitor of matrix metalloproteinases

TNF = Tumor necrosis factor

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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