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Chapter 6

THE ANTI-OXIDATIVE AND ANTI-INFLAMMATORY ROLES OF GALLIC ACID ON TRANSCRIPTIONAL REGULATION

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ABSTRACT

Gallic acid, a polyhydroxy phenolic compound, is found in various natural products such as tea leave, gallnuts, grapes, green tea, strawberries, lemons, pineapples and in red and white wines. Phenolic compounds are known to donate a proton from their hydroxyl (O–H) bond through hemolytic cleavage and form a stable phenoxy radical. Compounds possessing more than one phenolic hydroxyl group are further shown to generate an even more stabilized phenoxyl radical. As a result, gallic acid is regarded as an excellent antioxidant with a high free radical (reactive oxygen species or reactive nitrogen species-origin) scavenging effect. Among other properties, the anti-inflammatory, anti-bacterial, and antitumor properties are crucial. In this chapter, we mainly focus on the anti-oxidative and anti-inflammatory roles of gallic acid on transcriptional regulation of various cellular regulators. We will describe how gallic acid affects the suppression of anti-oxidative and anti-inflammatory regulators through the controlled regulation of key transcription factors. Since gallic acid and its esters can inhibit the TNFα-induced nuclear translocation of nuclear factor kappa-B (NF-κB) by way of a mechanism independent of inhibitors of kappa-B (IκB) degradation, we also deeply correlate the effect of gallic acid on the NF-κB-mediated transcriptional regulation of various early and late inflammatory mediators involved in related disease pathologies. In addition, we will focus on gallic acid's role on the epigenetic level since it exhibits potent p300/CBP-mediated anti-histone acetyl transferase (HAT) activity that inhibits the p65 acetylation-dependent NF-κB activation and production of inflammatory markers. Moreover, this review will show various gallic acid-mediated molecular targets, which affect signaling pathways within

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cells in different ways involving genetic or epigenetic mechanisms, and engage functional proteins in the formation of inhibiting complexes of strong affinities, ultimately perturbing the expression of oxidative and inflammatory molecules.

Keywords: Gallic acid, anti-inflammation, anti-oxidation, NF-κB, epigenetics, transcriptional regulation

INTRODUCTION

Gallic acid (GA) and its structurally related compounds are found in various natural products such as tea leaves, gallnuts, grapes, green tea, strawberries, lemons, pineapples and in red and white wines as its free or conjugated form with tannins. It is abundantly obtained by the solvent extraction of either nutgalls (*Quercus infectoria*, *Quercus stenophylla*) or Japanese gall (*Rhus javanica*) (Niho et al., 2001, p. 1,063). GA and its related compound are found in wine (Blanco et al., 1998, p. 327) and present as catechins in both green and black teas derived from the *Camellia sinensis* plant (Arce et al., 1998, p. 113; Constable et al., 1996, p. 189). Green tea contains polyphenols, consisting of flavanols, flavandiols, flavanoids, and phenolic acids, which make up 30% of dry weight materials in green tea (Graham, 1992, p. 334). A large proportion of the polyphenols contained in green tea are flavanols, commonly referred to as catechins.

The major catechins in green tea are (-) epigallocatechin-3-gallate (EGCG), (-) epigallocatechin, (-) epigallocatechin-3-gallate, (-) epicatechin, (+) gallocatechin, and (+) catechin (Graham, 1992, p. 334; Yang and Wang, 1993, p. 1,038). Among these polyphenols, ECGC is the most abundant one and is believed to be responsible for many of the beneficial effects of tea (Hour et al., 1999, p. 569; Kada et al., 1985, p. 127). In tea, GA may be present in free and esterified forms. Most of the GA found in black tea is derived originally from two flavanoids, epicatechin gallate and EGCG, which make up about 15% of the dry weight in the green tea leaf.

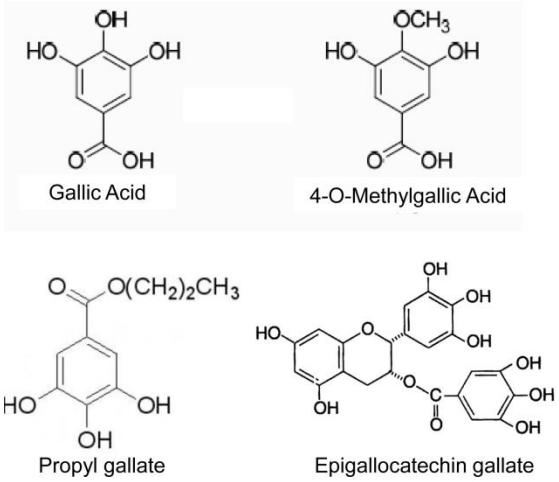

Figure 1. Structure of gallic acid and related compounds.

Approximately 35% of the mass of both epicatechin gallate and EGCG is GA, present as gallate esters (Wiseman et al., 1997, p. 705). Studies utilizing these compounds have found them to possess many potential therapeutic properties including antioxidant, anti-cancer (Chuang et al., 2010, p. 2,943) and anti-inflammatory activities (Kroes et al., 1992, p. 499).

As polyhydroxy phenolic compounds, GA and its related forms (Figure 1) are found in various natural products. Polyphenols are abundant micronutrients in our diet and are widespread constituents of fruits; vegetables; dry legumes; and beverages such as tea, coffee, or wine. Various molecules having a polyphenol structure have been identified in edible plants, and these molecules are classified into different groups as a function of the number of their phenol rings: the phenolic acids, flavonoids, stilbenes, and lignans (Manach et al., 2004, p. 727). In recent years, there has been a growing interest, supported by a large number of experimental and epidemiological studies (Dai and Mumper, 2010, p. 7,313; Middleton et al., 2000, p. 673; Scapagnini et al., 2011, p. 192), related to the beneficial effects of some phenolic substances against malignancies, cardiovascular diseases, and neurodegenerative diseases. Two classes of phenolic acids can be distinguished: derivatives of benzoic acid and derivatives of cinnamic acid. Hydroxyl-benzoic acids consist of GA, protocatechuic acid, and p-hydroxybenzoic acid. Among natural antioxidants, polyphenols successfully scavenge free radicals via their OH-groups (Hirano et al., 2001, p. 357). There is a high correlation between the content of phenolic substances and the total antioxidant activity of various plant extracts (Stratil et al., 2006, p. 607). Currently, GA (GA, 3, 4, 5-trihydroxybenzoic acid) and its derivatives are regularly applied in pharmaceutical and food industries (Lu et al., 2006, p. 263).

GA derivatives are exploited in phytomedicine, for example, as free radical scavengers, inducing the apoptosis of cancer cells (Saeki et al., 2000, p. 1,391) and interfering with the signal pathways associated with Ca^{2+} and oxygen radicals (Sohi et al., 2003, p. 221). GA and its derivatives also have a wide range of uses. Esters of GA, such as propyl gallate, octylgallate, lauryl gallate and dodecyl gallate, are commonly used as food additives and in cosmetics as antioxidants (van der Heijden et al., 1986, p. 1,067). Propyl gallate is also widely employed as an antioxidant in the pharmaceutical industry and is useful for preventing the deterioration and rancidity of fats and oils (van der Heijden et al., 1986, p. 1,067). GA has been investigated as a potential anticancer agent in various human cancer cell lines such as TE-2 (esophageal cancer), MKN-28 (gastric cancer), HT-29 and Colo201 (colon cancer), MCF-7 (breast cancer) and CaSki (cervix cancer) (Faried et al., 2007, p. 605). Additionally, previous studies have shown that GA-induced apoptosis in cancer cells is associated with oxidative stresses derived from reactive oxygen species (ROS), mitochondrial dysfunction and an increase in the intracellular Ca^{2+} level (Inoue et al., 2000, p. 1,153; Serrano et al., 1998, p. 350). However, the mechanism by which GA analogues induce apoptosis in some cell lines is not yet completely understood; the latter probably involving the paradoxical generation of ROS, which interferes with the homeostatic redox balance of the cell (Isuzugawa et al., 2001, p. 249). Furthermore, these compounds are excellent inhibitors of protein tyrosine kinases (PTKs) (Palacios et al., 2001, p. 527).

In another aspect, the amounts of GA in plant tissues may vary according to the plant species; however, it is recognized that external stimuli, such as UV radiation, microbial infections and chemical stressors such as glyphosate, may considerably alter the synthesis of these compounds (Daniel et al., 1999, p. 109). The complexity of determining health effects from the consumption of these food stuffs is therefore potentially augmented.

In this chapter, we mainly review the anti-oxidative and anti-inflammatory roles of GA, its esters, and gallic acid derivatives on the transcriptional regulation of various cellular regulators. We also focus on the effect of gallic acid on major transcription factors mediating the transcriptional regulation of various early and late inflammatory or oxidative mediators that are involved in related disease pathologies. In addition, the epigenetic role of GA for controlled transcription will also be discussed.

ANTI-INFLAMMATORY ROLE OF GALLIC ACID

Inflammation involves a complex web of intercellular cytokine signals. Activated monocytes and/or macrophages release a variety of inflammatory cytokines or mediators, such as tumor necrosis factor-α (TNF-α), interleukin- 1β (IL-1β), interleukin-6 (IL-6), reactive oxygen species (ROS), prostaglandin E2 (PGE2), and nitric oxide (NO), under physiological responses. These inflammatory cytokines and mediators regulate the functional activity of immune cells, and uncontrolled expressions are involved in the pathogenesis of many inflammatory diseases such as septic shock, hemorrhagic shock, multiple sclerosis, rheumatoid arthritis, ulcerative colitis, atherosclerosis, and cancer (Alfon et al., 1999, p. 325; Graeber and Streit, 2010, p. 89). It has been shown that inhibition in the production and biological activities of iNOS, COX-2, TNF-α, and IL-1β by selective inhibitors, neutralizing antibodies, or gene targeting resulted in a significant amelioration in the development of inflammation-mediated diseases such as rheumatoid arthritis, cardiovascular disease, and septic shock (Kagari et al., 2002, p. 1,459; Makarov, 2000, p. 441; Ohta et al., 2005, p. 180). Therefore, drugs that suppress the expression of these inflammation-associated genes have therapeutic potential for preventing inflammatory reactions and diseases.

There has been some evidence supporting GA's anti-inflammatory and pro-apoptotic activities (Kang et al., 2009, p. 760; Na et al., 2006, p. 1,597). GA treatment attenuates TNF-α and IL-6 expressions from human monocytes (Kuppan et al., 2010, p. 229). In addition, GA also inhibits mast cell-derived inflammation by suppressing pro-inflammatory cytokine expressions (Kim et al., 2006, p. 123). Recent reports showed that the expression levels of several important pro-inflammatory mediators from rheumatoid arthritis fibroblast-like synoviocytes were significantly suppressed by GA treatment (Yoon et al., 2012). We should now focus on how GA acts as an inflammatory antagonist. The answer lies in GA's role against key mediators of inflammation such as NF-κB, mitogen-activated protein kinases (MAPK), activator protein 1 (AP-1) etc.

NF-κB has a seminal role in immunity because NF-κB regulates the expression of many inflammatory genes encoding iNOS, COX-2, TNF-α, IL-1β, and IL-6 (Makarov, 2000, p. 441), which are involved in the pathogenesis of inflammatory diseases. Because of its critical role in inflammatory gene expression, NF-κB is a current target for treating various inflammatory diseases (Renard and Raes, 1999, p. 341). NF-κB, which is a heterodimer of a 50- and a 65-kDa subunit, resides as an inactive cytosolic protein due to its interaction with inhibitory proteins of the IκB family in most cell types, including blood monocytes. NF-κB activation is induced by a variety of stimuli, such as mitogens, cytokines, LPS, viruses, and UV light, which lead to the phosphorylation and the degradation of the IκB proteins (Mandrekar et al., 1999, p. 1,781). Most anti-inflammatory drugs have been shown to inhibit

inflammatory cytokine expression by inhibiting the NF-κB activation pathway (Castrillo et al., 2001, p. 15,854). It has been reported that n-propyl gallate exhibits anti-inflammatory activity through the NF-κB/IκB-α pathway (Jung et al., 2011, p. 352). In addition, prodelphinidin B-4 3′-O-gallate and other tea polyphenols consisting of gallocatechin and epigallocatechin-3-gallate were identified to be involved in the inhibition of COX-2 and iNOS via the down-regulation of the TGF-β- activated kinase (TAK1)/NF-κB pathway in LPS-activated RAW264.7 macrophage cells (Hou et al., 2007a, p. 742). Furthermore, 4-O-methylgallic acid, a major metabolite of GA, inhibited the expression of iNOS, COX-2, TNF-α, and IL-1β as well as the production of NO and PGE2 in LPS-stimulated macrophages and endotoxemic animals by blocking NF-κB activation through the inhibition of redox-sensitive IκB kinase activity (Na et al., 2006, p. 1,597). These studies suggest that the GA-mediated NF-κB pathway contributes to the anti-inflammatory effect and the prevention of human diseases through the suppression of inflammatory gene expression (Keifer et al., 2001, p. 22,382). Thus, as a NF-κB inhibitor, gallic acid could be a potential therapeutic drug in clinical applications to regulate the uncontrolled immune responses in inflammatory diseases.

We also found that *Terminalia chebula* (TC) extract component GA can inhibit IκBα degradation and phosphorylation, which leads to the prevention of NF-κB translocation and ultimately suppresses NF-κB activity and downregulates two key inflammatory genes, IL-8 and MCP-1, in high-level NF-κB-transfected Jurkat cells (Das et al., 2011, p. 927). In another study, we again demonstrated that the TC extract component GA significantly inhibited NF-κB activity and affected the proteomic profile of Jurkat cells. Consequently, TC extract component GA treatment mainly suppressed the expression of β-tubulin, RCHY1, IGF1R, and HSP70, which may negatively affect lymphoma cells. Furthermore, Ingenuity Pathways Analysis identified top-scoring proteins that are involved in molecular networks of immunological and inflammatory diseases (Das et al., 2012, p. 651). It has been reported that HSP70 has been shown to be a potent activator of the innate immune system, capable of inducing the secretion of pro-inflammatory cytokines (Asea et al., 2000, p. 435) via a NF-κB pathway (Chase et al., 2007, p. 6,818). In addition, positive feedback regulation of HSP70 induction exists in innate immune cells and induced pro-inflammatory cytokine secretion via Toll-like receptor 4 (TLR4) (Lee et al., 2013, p. 88). Therefore, suppressing the expression of HSP70 by TC extract component GA could be an effective approach in treating inflammatory diseases.

Vascular inflammation is a primary event in the pathogenesis of many human diseases, including atherosclerosis, hypertension, restenosis, and septic shock (Schiffrin, 2002, p. 115; Shah, 2003, p. 2,175). There is *in vivo* evidence of increased expressions of the intercellular adhesion molecules, endothelial adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in inflammatory animal models and in human atherosclerotic plaques (Cybulsky and Gimbrone, 1991, p. 788). In most resting cells, NF-κB is sequestered in the cytoplasm in an inactive form associated with IκB. Upon stimulation of endothelial cells by inflammatory cytokines, such as TNF-α, IκB becomes phosphorylated and proteolytically degraded; permitting NF-κB to translocate into the nucleus where NF-κB binds to κB enhancer elements of inflammatory target genes, including ICAM-1 and VCAM-1, to induce their transcription (Beg et al., 1993, p. 3,301; Chen et al., 1995, p. 3,538). The latter evidence suggests that a selective suppression of the NF-κB signaling pathway prevents various inflammatory diseases including inflammatory atherosclerosis. A variety of natural substances, such as hematein and gallates, have been reported to possess anti-atherogenic

properties (Choi et al., 2003, p. 287; Murase et al., 1999, p. 1,412). These compounds have been shown to inhibit the cytokine-induced expression of ICAM-1 and VCAM-1 in endothelial cells, probably by inhibiting NF-κB activation. Furthermore, 4-O-methylgallic acid prominently reduces the expression of ICAM-1 and VCAM-1 and also the adhesion of monocytes to TNF-α-treated human umbilical vein endothelial cells by inhibiting the redox-sensitive DNA-binding activity of NF-κB. These results indicate that these compounds have the potential to treat human vascular inflammatory diseases including atherosclerosis.

It is reported that grape seed extract containing GA, catechin, epigallocatechin gallate, and proanthocyanidin is shown to prevent amyloid beta (Aβ) deposition and attenuate inflammation in the brain of a mouse with Alzheimer disease (Wang et al., 2009, p. 3). GA also possesses potent anti-histone acetyltransferase (HAT) activity and inhibits RelA acetylation by directly inhibiting the activity of HAT enzymes, which finally leads to the downregulation of NF-κB function via diverse anti-inflammatory signals (Choi et al., 2009b, p. 2,011). Additionally, GA can efficiently block neuronal cell death by downregulating the expression of cytokines and the *in vivo* expression level of NF-κB acetylation (Kim et al., 2011, p. 1,798).

Mast cells, which are constituents of virtually all organs and tissue, are important mediators of allergic reactions. Immediate hypersensitivity (anaphylaxis) is mediated by histamine release in response to the antigen cross-linking of immunoglobulinE (IgE). Mast cell activation causes the process of degranulation, resulting in the release of mediators, such as histamine and an array of inflammatory cytokines (Church and Levi-Schaffer, 1997, p. 155). Among the inflammatory substances released from mast cells, histamine remains the best-characterized and most potent vasoactive mediator implicated in the acute phase of immediate hypersensitivity (Petersen et al., 1996, p. 672). Therefore, histamines are one of the targets for agents to suppress their expressions and/or activities, which could arrest the inflammation. GA efficiently suppressed histamine releases and proinflammatory cytokine production in mast cells (Kim et al., 2006, p. 123). Additionally, GA decreases the histamine release from rat basophilic leukemia cells and suppresses pro-inflammatory cytokine production in murine peritoneal macrophages (Kwon et al., 2004, p. 436; Matsuo et al., 1997, p. 58).

Matrix metalloproteinases (MMPs), zinc-dependent proteolytic enzymes, play an important role in the outcome of an inflammatory reaction, angiogenesis, and tissue remodeling, and cause the release of extracellular matrix-bound growth factors and cytokines that regulate many of these processes (Mott and Werb, 2004, p. 558). MMP-9, which is the 92-kDa gelatinase B expressed molecule in various cell lines, such as keratinocytes, osteoclasts, eosinophils, neutrophils, and macrophages, are increased and activated in many kinds of inflammatory and malignant diseases (Sorsa et al., 2006, p. 306). Therefore, MMPs are one of the targets for agents to suppress their expression and/or activities and could arrest the inflammation. Inhibition of MMP-9 activity by n-propyl gallate supports its anti-inflammatory activities (Jung et al., 2011, p. 352). However, how n-propyl gallate inhibits MMP-9 activity remains to be elusive. In addition, epigallocatechin-3-gallate has been found to inhibit the expression and secretion of MMP-9 in macrophage-differentiated HL-60 myeloid leukemia cells (Annabi et al., 2007, p. 1,277).

A mitogen-activated protein kinases (MAPKs) cascade is one of the important signaling pathways in immune responses (Arbabi and Maier, 2002, p. 74). The expression of TNF-α and IL-6 is also regulated by MAPKs. The exact signaling pathways among three types of

MAPKs, such as p38, ERK, and JNK, are still unclear; however, p38 MAPK is thought to play an important role in the regulation of inflammatory responses. Activation of p38 MAPK is essential for the expression of the pro-inflammatory cytokines (Manthey et al., 1998, p. 409). Interestingly, the idea is supported that GA has the inhibitory activity on p38 MAPK activation and downstream TNF-α and IL-6 production (Kim et al., 2006, p. 123). Although GA acts as a potent inhibitor of NF-κB and its derivative, epigallocatechin-3-gallate has been shown to suppress NF-κB activation and phosphorylation of p38 MAPK and JNK1/2 in human astrocytoma U373MG cells (Kim et al., 2007, p. 587). Moreover, prodelphinidin B-2 3,3′di-O-gallate, a green tea proanthocyanidin, results in the inhibition of COX-2 via the suppression of activated-MAPKs, including JNK, ERK, and p38 MAPK, and the subsequent blockage on the MAPK-mediated activation of NF-κB, and AP-1 and CCAAT/enhancer-binding protein (C/EBP) δ (Hou et al., 2007b, p. 67). In addition, GA-related polyphenol compounds, epigallocatechin-3-gallate and the aflavin-3, 3'–digallate also inhibit the activation of MAPKs (Chung et al., 2001, p. 2,022).

The transcription factor AP-1 has a pivotal role in a variety of physiological processes such as growth regulation, apoptosis, cell transformation, inflammation, innate immune response and tumor metastasis (Bohmann et al., 1987, p. 1,386; Eferl and Wagner, 2003, p. 859). It is being reported for the first time that the ethyl gallate attenuate LPS induced ICAM-1 and VCAM-1 through the modulation of AP-1 activity (Mehla et al., 2011, p. 1,345) where cell adhesion molecules, such as ICAM-1 and VCAM-1, were involved in the immune response by allowing leukocyte endothelial interaction and their subsequent migration at the site of insult (Luscinskas and Gimbrone, 1996, p. 413; Meager, 1999, p. 27). This suggests that the potential inhibition of AP-1 activity by GA or its ester could be relevant in the prevention of a number of diseases where AP-1 activation is involved in disease pathogenesis. Furthermore, it can also be useful for conditions where both AP-1 and NF-κB act coordinately (Naugler and Karin, 2008, p. 19; Shaulian and Karin, 2002, p. 131) in inflammatory diseases. In this context, by using a combinatorial approach, GA along with other NF-κB inhibitors may provide improved therapeutic efficacy for inflammatory-related diseases like atherosclerosis, asthma, acute lung injury, etc.

ANTI-OXIDATIVE ROLE OF GALLIC ACID

Free radicals in the human body can cause well recognized, harmful effects and are being continuously investigated. Free radical species viz. hydroxyl, nitric oxide (NO), superoxide work in an intricate way in biological systems and their overproduction deleteriously affects the membrane lipids, cellular proteins and enzymes, ultimately resulting in oxidative stress. This oxidative stress causes cell death and eventually leads to inflammatory disorders, cancer, diabetes, etc. A pathway leading to the activation of transcription factor NF-κB, a regulator of inflammation, is also under ROS-mediated control. Therefore, antioxidant compounds could have anti-inflammatory activities (Bubici et al., 2006, p. 6,731). Synthetic compounds viz. butylatedhydroxytoluene (BHT) and butylatedhydroxyanisole (BHA) are well known antioxidants, but are also carcinogenic (Ito et al., 1983, p. 343). Natural products from the plant sources are relatively safe and have immense potential to display over whelming

biological activities which depend upon their nature, structure and interactions with other molecules in the assortment (Djeridane et al., 2006, p. 719).

Antioxidants preventing free-radical reactions attract intense scientific and economic interest in human health, (Aruoma et al., 1997, p. 389) food, and polymer industries (Balasundram et al., 2005, p. 319). Antioxidants, at low concentrations, delay or prevent molecular deterioration by adverse radical reactions and radical-related oxidation and protect the human body against damage by reactive oxygen species (Halliwell, 1996, p. 439). GA has been demonstrated to have a broad spectrum of biological activities, including antimicrobial, anti-inflammatory, and anti-oxidative activities.

Additionally, previous studies have shown that GA-induced apoptosis in cancer cells in association with oxidative stresses derived from reactive oxygen species (ROS), mitochondrial dysfunction and an increase in intracellular Ca^{2+} levels (Inoue et al., 2000, p.1,153; Serrano et al., 1998, p. 49). GA exhibiting antiapoptotic potential in normal human lymphocytes is well established (Li et al., 2005, p. 230); however, as a strong natural antioxidant scavenging ROS, GA's role is well reported in several studies (Abdelwahed et al., 2007, p.1; Lu et al., 2006, p. 263).

Reactive oxygen species (ROS) play a direct role in the pathogenesis of different disease conditions including inflammation, burns and neurodegenerative diseases (Basha and Madhusudhan, 2010, p. 1,017). It is well known that fluoride accumulation in tissues leads to an oxidative stress condition through increasing ROS production and suppressing endogenous antioxidant enzyme systems (Ranjan et al., 2009, p. 900). Recently, it has been suggested that GA ameliorated sodium fluoride induced an oxidative state in a rat brain (Nabavi et al., 2013, p. 261). Neuroprotective activities of GA against 6-hydrodopamine auto-oxidation- induced apoptosis in human SH-SY5Y cells (Lu et al., 2006, p. 263) and amyloid beta protein (25–35)-induced toxicity in cultured rat cortical neurons (Ban et al., 2008, p. 149) have been previously reported. Treatment with GA leads to an increase in glutathione (GSH) levels and a reduction in oxidized glutathione (GSSG). It is well known that the GSH/GSSG ratio enhancement by gallic acid is enhanced with the addition of the hydroxyl groups (Kim, 2007, p. 587). The presence of a hydroxyl group at a para position to the COOH group is responsible for the antioxidant activity of GA derivatives and may explain the protective mechanism against sodium fluoride-induced oxidative stress.

The accumulation of advanced glycation end products (AGEs), which are the product of the non-enzymatic glycation of proteins, plays a major role in stiffening the cardiac tissues and eventually leads to fibrosis (Ahmed, 2005, p. 67). The formation and accumulation of AGEs have been widely distributed for their key role in promoting vascular dysfunction and other complications. These AGEs impair cellular functions by binding to its receptor for AGEs (RAGE) (Forbes et al., 2008, p. 1,446) through the activation of NF-κB and MAPKs (Bierhaus et al., 2005, p. 876). The activation of RAGE induces an oxidative stress and a series of inflammatory process such as the up-regulation of cytokines and various adhesion molecules (Schleicher and Friess, 2007, p. 17). Dietary plants with abundant antioxidant phenolics have the potential to function as powerful anti-glycation agents in blocking the AGEs-induced toxicities (Farrar et al., 2007, p. 193). In this context, GA also receives much attention because of its potent free radical scavenging and anti-oxidant activities. Consistent with this concept, recently, GA has exhibited a protective role against AGEs-induced cardiovascular complications, probably through its free radical scavenging activity (Umadevi et al., 2012, p. 304).

Glutahione (GSH) is mainly involved on the synthesis of important macromolecules by conferring protection against reactive oxygen species. GSH contributes to the maintenance of the antioxidant activities of other antioxidant enzymes, such as glutathione peroxidase as well as vitamins C and E (Johansen et al., 2005, p. 5). In this regard, an increased concentration of superoxide dismutase, catalase, and GSH contents on the GA pretreatment implicates an augmentation in antioxidant capacity and reduced per oxidation in the membrane lipids on the GA pretreatment in cardiovascular complications (Umadevi et al., 2012, p. 304). Similar results were observed in cells induced with high glucose content with a concomitant depleted level of GSH (Niedowicz and Daleke, 2005, p. 289) and the restoration of a redox status in cells on the GA pretreatment in cultured human THP-1 monocytes (Kuppan et al., 2010, p. 229).

It is reported that GA induces the expression of several antioxidant enzymes, such as thioredoxin-1 (TXN), thioredoxin reductase 1 (TXNRD1), antioxidant enzyme 372 (AOE372), glutathione synthetase (GSS); and DNA repair molecules such as Ligase 4 (LIG4), DNA polymerase delta subunit 2 (POLD2), methylpurine DNA N-glycosylase (MPG), growth arrest and DNA-damage-inducible alpha (GADD45A), proliferating-cell nuclear antigen (PCNA), replication protein A 32 kDa subunit (RPA2), DNA damage-inducible transcript 3 protein (DDIT3), hemeoxygenase 2 (HMOX2), xero-dermapigmentosum, complementation group A (XPA), thymine-DNA glycosylase (TDG), excision repair cross-complementation group 1 (ERCC1), general transcription factor IIH, polypeptide 1 (GTF2H1). GA also induces the repression of glutathione peroxidase 1 (GPX1), selenoprotein W 1 (SEPW1), DNA polymerase delta subunit 1 (POLD1), and SHC-transforming protein 1 (SHC1) gene expressions using microarray expression profiling (Abdelwahed et al., 2007, p. 1). Previous studies investigated that mice lacking SHC display a prolonged life span, reduced production of intracellular oxidants, and an increased resistance to oxidative stress-induced apoptosis (Migliaccio et al., 1999, p. 309).

Accordingly, the majority of studies using SHC $^{-/-}$ mice have defined the pathophysiological role of SHC in cardiovascular disease where ROS represents a substantial triggering component (Camici et al., 2007, p. 5,217; Cosentino et al., 2008, p. 622). Other authors have also reported that another protein, such as TXN, is a highly conserved protein and has been recognized as a critical protection system against oxidative stress (Forstermann, 2008, p. 338). Such results suggest that pretreatment with GA exhibits a protective role against oxidative stress-induced apoptosis as well as physiological complications.

SUPPRESSIVE ROLE OF GALLIC ACID FROM AN EPIGENETIC PERSPECTIVE

Epigenetic refers to any heritable influence (in the progeny of cells or individuals) on the chromosome or gene function that is not accompanied by a change in DNA sequence, constituting an important mechanism by which dietary components can selectively activate or inactivate gene expression (Davis and Ross, 2007, p. 88). Epigenetic mechanisms include changes in DNA methylation, histone modifications, and altered microRNA (miRNA) expression (Winter et al., 2009, p. 228; Yoo and Jones, 2006, p. 37). Changes to the structure of chromatin influence gene expression by either inactivating genes, which occurs when the

chromatin is closed (heterochromatin), or by activating genes when the chromatin is open (euchromatin) (Rodenhiser and Mann, 2006, p. 341). The nucleosome, which is the fundamental repeating unit of chromatin, is composed of DNA wrapped around a histone octamer, formed by four histone partners, an H3-H4 tetramer, and two H2A-H2B-dimers. Each successive nucleosomal coreis separated by a DNA linker associated with a single molecule of histone H1. Chromatin modifications usually occur at the amino acids of the N-terminal tails of histones and either facilitate or hinder the association of DNA repair proteins and transcription factors with chromatin. These core histones undergo a wide range of post-translational modifications, including: acetylation, controlled by histone acetyltransferases (HATs) associated with gene expression (Zhang and Dent, 2005, p. 1,137); deacetylation, controlled by histone deacetylases (HDACs) associated with gene inactivation; and methylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation, and possibly biotinylation (Davis and Ross, 2007, p. 88).

Among various epi-modifiers, GA acts as a potent HAT inhibitor. HATs, enzymes that acetylate conserved lysine aminoacids on histone proteins by transferring an acetyl group from acetyl CoA to form e-N-acetyl lysine, are other important targets for dietary components. HATs include atleast 25 members and are organized into 4 families based on primary structure homology (Lee and Workman, 2007, p. 284). Several studies have recently reported that GA is a potent HAT inhibitor. GA, an organic acid found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants, can uncompetitively inhibit p300/CBP-dependent HAT activities, increase the level of cytosolic IκBα, prevent lipopolysaccharide (LPS)–induced p65 translocation to the nucleus, and suppress LPS-induced NF-κB activation in A549 lung cancer cells (Choi et al., 2009b, p. 2,011).

Furthermore, they showed that gallic acid inhibits the acetylation of p65 and LPS-induced serum levels of interleukin-6 *in vivo*. The same group also examined the biological effect of GA as a HAT inhibitor (HATi) on Aβ-induced neuroinflammation and neuronal cell death, which were triggered by activated microglia. Furthermore, GA-pretreated mice showed a restoration of altered behavior and Aβ-induced memory impairment. They also found that GA inhibited NF-κB-mediated cytokine production in the brain by blocking RelA acetylation (Kim et al., 2011, p. 1,798). EGCG, the major polyphenol found in green tea, is reported to have an anti-NF-κB transactivation activity in a broad range of human malignancies such as colon cancer, lung cancer, breast cancer, and in chronic inflammation (Doss et al., 2005, p. 259; Yang et al., 2005, p. 135). EGCG has been shown to inhibit the production of nitric oxide synthase (NOS2) by blocking the NF-κB signal transduction pathway (Chan et al., 1997, p. 1281). EGCG is also known to suppress NF-κB activation and phosphorylation of the p38 mitogen-activated protein kinase and c-Jun NH2-terminal kinase (Kim et al., 2007, p. 587).

Furthermore, EGCG reduces the binding of p300 to the promoter region of the IL-6 gene with an increased recruitment of HDAC3, which highlights the importance of the balance between HATs and histone deacetylases in the NF-κB–mediated inflammatory signaling pathway (Choi et al., 2009a, p. 583).

DNA methylation, another epigenetic mechanism is a heritable modification of the DNA structure that does not alter the specific sequence of base pairs responsible for encoding the genome but that can directly inhibit gene expression (Das and Singal, 2004, p. 4,632). A DNA hypermethylation of CpG islands is usually associated with a silencing of the expression of genes in contrast to a loss of methylation, which often leads to gene

reactivation. Abnormal patterns of methylation DNA may ultimately lead to genetic instability and cancer development through the epigenetic inactivation of certain critical cancer-related genes by promoter hypermethylation. These altered genes include tumor suppressor genes, such as the cell cycle checkpoint genes, $p21^{WAF1/CIP1}$ and $p16^{INK4a}$, and growth regulatory genes, such as the RAS association domain family 1A (*RASSF1A*) and retinoic acid receptor β (*RARβ*) (Baylin and Ohm, 2006, p. 107). DNA methylation is regulated by DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b) in the presence of S-adenosyl-methionine, which serves as a methyl donor for the methylation of cytosine residues at the C-5 position to yield 5-methylcytosine (Herman and Baylin, 2003, p. 2042).

Although the role of GA on DNA methylation is yet to be disclosed, GA-related compounds, such as EGCG, exhibit a potential demethylating agent. The generation of S-adenosyl-S-homocysteine, a potent inhibitor of DNA methylation, is one of the mechanisms for the demethylating properties of this compound. EGCG can form hydrogen bonds with different residues in the catalytic pocket of DNMT and thus act as a direct inhibitor of DNMT1 (Fang et al., 2003, p. 7,563). Other groups reported that cancer inhibition generated from dietary EGCG is associated with gene reactivation through demethylation in the promoters of methylation-silenced genes such as $p16^{INK4a}$, *MGMT*, *hMLH1*, *GSTP1*, *WIF-1*, *RECK*, and *RARβ*.

The effects of dietary EGCG on DNMTs appear to be associated with direct inhibition from interactions with the catalytic site of the DNMT1 molecule, and may also indirectly influence the methylation status through metabolic effects associated with energy metabolism (Gao et al., 2009, p. 2,025; Kato et al., 2008, p. 647). Therefore, a reversal of the hypermethylation-induced inactivation of key tumor suppression genes by dietary DNMT inhibitors, such as GA or EGCG, could be an effective approach for cancer-inflammation prevention and therapy.

MicroRNAs are an evolutionary conserved class of ~22 endogenous nucleotide noncoding RNAs which are involved in post-transcriptional gene repression (Taganov et al., 2006, p. 12,481). MicroRNAs are being investigated for their role as post-transcriptional regulators of pro-inflammatory genes. MicroRNAs suppress protein synthesis by inhibiting the translation of proteins from mRNA or by promoting the degradation of mRNA, thereby silencing the gene expression. Certain miRNAs were discovered to be involved in various physiological and pathological processes such as vascular inflammation (Gantier et al., 2007, p. 458). Previous studies have demonstrated that miR-126 inhibited the expression of VCAM-1; therefore, decreasing miR-126 in endothelial cells increases TNF-α-stimulated VCAM-1 expression and enhances leukocyte adherence to endothelial cells (Urbich et al., 2008, p. 581). Recently, it has been demonstrated that polyphenolic red wine extract GA increased miR-126 and consequently decreased the mRNA expression of LPS-induced inflammatory mediators NF-κB, ICAM-1, VCAM-1 and platelet endothelial cell adhesion molecules (PECAM-1), indicating the potential role of miR-126 in the anti-inflammatory properties in human colon-derived CCD-18Co myofibroblast cells (Angel-Morales et al., 2012, p. 745). In addition, EGCG has also been found to modulate miRNA expression in human hepatocellular carcinoma HepG2 cells. A microarray analysis of the HepG2 cell line after EGCG treatment has revealed that EGCG modified the expression of 61 miRNAs. Furthermore, miR-16, which is one of the miRNAs up-regulated by EGCG treatment, is confirmed to mediate the EGCG induction of apoptosis in human hepatocellular carcinoma cells by targeting Bcl-2 (Tsang and Kwok, 2010, p. 12,481).

CONCLUSION

Currently, plant polyphenols GA and related compounds, the regular consumption of which have been claimed to be beneficial for human health, have achieved a greater recognition not only for anti-tumor, anti-inflammatory, anti-oxidative properties, but also for their presence and vast abundance in fruits, seeds, derived food stuffs and beverages. Here, we mainly review the anti-oxidative and anti-inflammatory roles of gallic acid and focus on key transcription factors, such as NF-κB, MAPK, and AP-1, for the suppression of major anti-oxidative and anti-inflammatory regulators. The effect of gallic acid on NF-κB, MAPK, and AP-1-mediated transcriptional regulation of various inflammatory mediators involved in related disease pathologies has been discussed in this review. The epigenetic role of gallic acid has also been investigated: it exhibits potent p300/CBP-mediated anti-histone acetyl transferase (HAT) activity that inhibits the p65 acetylation-dependent NF-κB activation and production of inflammatory markers; a gallic acid-related compound, EGCG, exhibits a potential demethylating agent; finally, the affect of GA on mir-126 expression resulted in a decreased expression of various inflammatory mediators such as NF-κB, ICAM-1, VCAM-1, and PECAM-1. Further research is necessary to determine whether, and to what extent, GA plays an epigenetic role as an anti-inflammatory and anti-oxidative molecule.

Moreover, our study suggests various gallic acid-mediated molecular targets (Figure 2), which affect signaling pathways within cells in different ways involving genetic or epigenetic mechanisms.

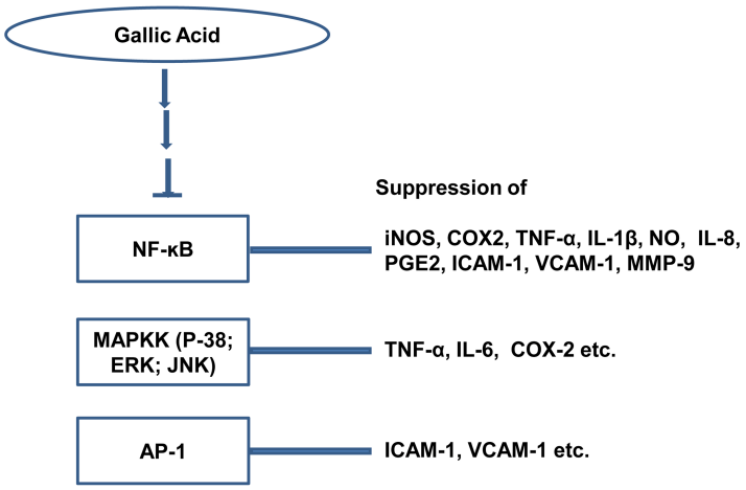

Figure 2. Possible site of action and targets of gallic acid.

The mechanisms underlying the anti-oxidative and anti-inflammatory effects of gallic acid are multifactorial, and it is likely that multiple molecular mechanisms, rather than a single receptor or molecular target, are involved. It is reasonable to suggest that gallic acid initially binds to one or more of the target proteins, which may be transmembrane receptors, kinases or other enzymes. These actions may inhibit key signaling and metabolic pathways that are essential for the development of inflammation and oxidative stress. Knowledge gained from the studies on the biological properties and activities of gallic acid reviewed in

this article will be useful in the design of prospective studies and in the selection of target biomarkers for intervention trials against inflammation and oxidative stress.

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