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Antioxidative and anti-inflammatory activity of functional foods

Chi-Cheng Lu[1] and Gow-Chin Yen[1,2]

Chronic inflammation is linked to numerous human diseases, and this response shows no condition-specific benefits for human health. Dietary intake of antioxidant products is a strategy and an emerging trend for combatting the inflammatory responses of chronic diseases and their risk factors. In this paper, we review recent studies that have examined the potential molecular signaling of antioxidants and the anti-inflammatory effects of individual dietary phytochemicals from popular foods and drinks (e.g. curcumin, EGCG, astaxanthin, and lutein). The protective effects of these phytochemicals are explored using *in vitro* cell culture and *in vivo* animal models. Therefore, this review is being undertaken to support the health implications and elucidate our understanding of the natural bioactive substances with antioxidant and anti-inflammatory properties.

Addresses
[1] Department of Food Science and Biotechnology, National Chung Hsing University, 250 Kuokuang Road, Taichung 40227, Taiwan
[2] Agricultural Biotechnology Center, National Chung Hsing University, Taichung 40227, Taiwan

Corresponding author: Yen, Gow-Chin (gcyen@nchu.edu.tw)

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Introduction

The pathophysiological phenomenon of inflammation is a process regulated through the activation of several immune cells and involves several inflammatory mediators, including interleukin-1 beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), nitric oxide (NO), and prostaglandin E2 (PGE2) [1,2]. Therefore, pro-inflammation can cause a variety of diseases such as cancer, atherosclerosis, neurological diseases and diabetes, and presents as a complex defense response with immunomodulation after injurious stimuli [2,3••]. It is documented that excessive production of inflammatory stimuli in a site of the human body might lead to chronic diseases or cancer [4]. In addition, the production of reactive oxygen species (ROS, i.e. O_2^-, H_2O_2) is found to cause oxidative stress in sites of chronic inflammation [5,6]. ROS production is involved in vital signal transduction and acts as a mediator which modulates gene expression to induce potentially toxic responses [6]. The ROS production which is mediated by NADPH oxidase (NOX) damages the microenvironment in host tissue and results in a pro-inflammatory phenomenon with release of cytokines such as IL-1β and TNF-α through the nuclear factor kappa B (NF-κB)-dependent mechanism [7,8]. Importantly, it is well-documented that phytochemicals or dietary bioactive compounds from functional foods are considered to have beneficial outcomes against chronic inflammation and to possess antioxidant properties [9].

Recently, an increasingly positive trend has been observed in the consumption of and interest in antioxidant or anti-inflammatory products obtained from natural foods or dietary bioactive components for health-related purposes [10•,11,12]. There have been many studies aimed at examining numerous dietary ingredients [e.g. curcumin, epigallocatechin gallate (EGCG), astaxanthin, lutein] which have biological effects and are readily available. In previous studies, these active compounds are reported to exert potent biological effects and have biomedical applications [3••,13–15]. These substances have been investigated with a focus on the anti-inflammatory or antioxidant effects involved in preventing ROS from attacking DNA. It is deemed that curcumin, found in turmeric, plays a central role in the modulation of antioxidant effects and cellular inflammation [3••,16]. In the United States, curcumin is a popular nutraceutical supplement in markets and has been extensively researched. Furthermore, green tea is a widely consumed beverage, and people who like the tea are growing considerably. EGCG is rich in green teas and has various and prominent biological effects [13]. Lutein and astaxanthin are served as carotenoids and have unique anti-inflammatory health benefits related to vision and eye diseases [14,15,17]. In the following sections, we review the most recent literatures related to the anti-inflammatory and antioxidant activity of the abovementioned phytochemicals found in popular foods and drinks, and summarize the underlying molecular signaling of these dietary compounds (curcumin, EGCG, astaxanthin, and lutein) using *in vitro* and *in vivo* models to clarify their chemopreventive effects.

Antioxidative and anti-inflammatory effects of curcumin

Curcumin is an active polyphenol found in the spice turmeric and other traditional herbal powders [3••,16]. Extensive

research has demonstrated that curcumin is involved in a vast number of promising biological activities and is effective in controlling antioxidant and anti-inflammatory effects, with therapeutic potential for preclinical treatments [3••]. Guo *et al.* [18] showed that curcumin reduced ROS production and inhibited inflammatory mediators [TNF-α and monocyte chemoattractant protein-1 (MCP-1)] in HIV-1-gp120-stimulated murine microglial N9 cells, preventing neuronal damage. Curcumin also attenuated the delayed rectification and transient outward potassium current in primary rat cortical neurons. Liu *et al.* [19] found that curcumin exhibited a protective effect against acrolein-induced cell death through mitochondrial dysfunction in a human retinal pigment epithelial cell line (ARPE-19). Curcumin also significantly suppressed a decrease in glutathione (GSH) content and glutathione S-transferase (GST) activity as well as an increase in the ROS level in ARPE-19 cells after induction by acrolein. Notably, curcumin dramatically blocked hydrogen peroxide (H_2O_2)-induced ROS in human bone marrow-derived mesenchymal stem cells, it protected the antioxidant enzyme (glutathione peroxidase, GPx) and it reduced apoptotic death triggered by pre-treatment with H_2O_2 [20]. Han *et al.* [21•] further observed that curcumin initiated a biological effect of autophagy against oxidative stress caused by H_2O_2 exposure in human umbilical vein endothelial cells (HUVECs) through alteration of the PI3K/AKT/mTOR signaling pathway and suppression of FOXO1 nuclear localization. In endothelial cell oxidative stress, curcumin was reported to protect HUVECs from H_2O_2-caused oxidative stress injury *via* inhibition of Notch signaling to attenuate endothelial cell apoptosis [22]. *In vitro* studies of mouse macrophage RAW 264.7 cells induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), curcumin diminished inflammatory effects by reducing not only NF-κB and IL-1β expression but also aldose reductase activity [23••]. Curcumin also exhibited an antioxidant effect through inhibition of lipid peroxidation and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical formation as well as suppression of 2,2′-azino-*bis*(3-ethylbenzthiazoline-6-sulfonic acid) radical generation [23••]. Zhong *et al.* [24] reported that curcumin reduced lipopolysaccharides (LPS)-induced ROS generation in RAW 264.7 macrophages that resulted from the increased expression of heme oxygenase-1 (HO-1) and the inhibition of MCP-1 expression. However, curcumin also enhanced the effect of oxidative stress through targeting of the cytosolic/nuclear thioredoxin system and thioredoxin reductase 1 (TrxR1), which played a vital role in sensitizing cytotoxicity in HeLa cells [25].

The effect of curcumin application on inflammatory processes was also evaluated through *in vivo* experiments. Kant *et al.* [16] showed that curcumin treatment at 0.3% (400 μl) promoted wound contraction and reduced the release of inflammatory cytokines such as TNF-α and IL-1β in diabetic rats. However, curcumin enhanced IL-10 (an anti-inflammatory cytokine) and antioxidant enzymes (SOD, catalase and GPx). Curcumin (50 mg/kg body weight per day) significantly reduced the TNF-α and IL-6 levels in rats after cadmium administration. The impairment of protective biomarkers of oxidative status caused by cadmium was modulated by curcumin [26]. Gao *et al.* [27] also indicated that curcumin at 200 mg/kg moderated the reduction of serum and hepatic GSH as well as the elevation of hepatic MDA, serum alanine amino transferase (ALT), and aspartate aminotransferase (AST) levels in arsenic-treated mice. Curcumin (200 mg/kg) stimulated the expression of hepatic NF-E2-related factor 2 (Nrf2) and its known downstream genes [NAD(P)H:quinone oxidoreductase 1 (NQO1) and HO-1] in mice with hepatotoxicity and oxidative injuries after arsenic exposure. The study observed an additional protective feature of curcumin involving the reduction of the damage caused by experimental sepsis in rats. Curcumin also decreased serum TNF-α and IL-1β levels, as well as tissue MDA and myeloperoxidase (MPO) levels by preventing inflammation [28]. Wang *et al.* [29] showed that curcumin (300 mg/kg body weight given orally) decreased hepatic fibrosis in BALB/c mice induced by thioacetamide by promoting hepatic stellate cell activation and reducing apoptosis of damaged hepatocytes, resulting in anti-inflammatory responses. This anti-inflammatory effect is mediated through regulation of p53 as well as Bax and Bcl-2 mRNA expression in the animal model of hepatic fibrosis. Interestingly, in heat-stressed quail, increased curcumin supplementation at 200 or 400 mg/kg of the diet both improved quail performance and activated Nrf2/HO-1-dependent signaling to prevent oxidative stress-mediated cellular damage [30].

Results of the abovementioned studies suggest that curcumin has therapeutic potential across a wide range of illnesses for *in vitro* and *in vivo* observations involved in antioxidant and anti-inflammatory activities. Curcumin also reduces inflammatory disease risk thereby helping achieve human health maintenance. Thus, there is evidence that curcumin likely plays a crucial role in modulating inflammation by targeting and suppressing NF-κB and other related pro-inflammatory factors. Moreover, the antioxidant health effects of curcumin specifically help suppress inflammatory response factors.

Antioxidative and anti-inflammatory effects of EGCG and epicatechin

Extensive research has shown that tea catechins which are found in green tea and dietary foods contain a series of bioactive compounds and possess chemopreventive properties [13,31]. EGCG is considered a powerful and abundant catechin that exerts antioxidant and anti-inflammatory functions via up-regulation of genes encoding for phase II enzymes (GST and NQO1) with antioxidant response elements (ARE) in the promoter